ACTA RADIOLOGICA

EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE ET SUECIAE

VOL. 55 FEBRUARY 1961 FASC. 2

PRIMARY CHONDROSARCOMA OF BONE

by

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The histologic diagnosis of chondrosarcoma of bone is difficult and rests upon an appreciation of the subtle morphologic criteria of well differentiated forms of cartilaginous tumors; most chondrosarcomas are well, or moderately well, differentiated. The majority of chondrosarcomas are so situated that adequate surgical treatment may mean loss of part or the whole of a limb and at times hemipelvectomy; a correct diagnosis therefore becomes of the greatest importance. A group of essentially untreated, biopsy-proved, chondrosarcomas and a group that was surgically treated are described and discussed with special reference to the evolution and course of the tumour.

Thirty-nine cases of chondrosarcomas from the bone tumor registry of Karolinska Sjukhuset have been studied from the clinical, pathologic and roentgenologic standpoints and carefully investigated so as to exclude osteosarcomas, benign cartilaginous tumors, and the benign tumors that may be confused with chondrosarcomas. Sixteen of the cases received no surgical treatment for various reasons e. g. pathologic underestimation of the malignancy of the tumor, age, poor health, or reluctance to carry out radical surgical procedures; all of the 16 received irradiation therapy. The tumors of the remaining 23 cases were treated surgically either by local removal or amputation of the affected part; 9 of these cases also received irradiation therapy either

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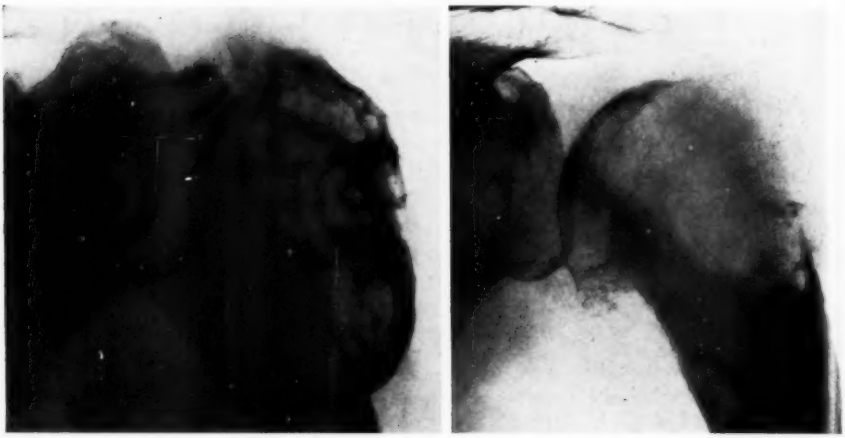

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Fig. 1. a) Peripheral chondrosarcoma, grade II, in man aged 68, arising in large osteochondroma in proximal metaphysis of humerus. b) Invasion of proximal end of humerus by tumor after curettage.

pre-operatively, postoperatively, or both. All of the 39 cases were followed for at least five years or until death.

Of the 39 patients, 25 were male and 14 were female. The average age of onset of symptoms for the entire group was 46 years, with an age span of 15 years to 84 years. The average age differs between the men and the women, being 51 and 36 years respectively. For the patients with peripheral tumor the mean age was 38 years and for the patients with central tumor it was 52 years.

As in other reported series (DAHLIN & HENDERSON, JAFFE, O'NEAL & ACKERMAN) of chondrosarcomas the majority of the tumors in our cases involved the long bones, especially the femur, and the bones of the pelvis (Table 1). Two of the chondrosarcomas arose in the bones of the hand, a phalanx of an index finger and a metacarpal. These two cases have been reported in detail previously (JACOBSSON & SPJUT) 1960. Most chondrosarcomas may be classified as central or peripheral, a designation suggesting an origin within a bone or in a peripheral part or surface of a bone. In either case the sarcoma may have arisen de novo or from a pre-existing benign cartilaginous tumor. It is commonly difficult satisfactorily to demonstrate the latter event (Fig. 1). Among our cases there were 20 central tumors, 13 peripheral tumors, and 6 that were uncertain. The classification as to a central or peripheral location was based mainly upon the roentgenographic findings. Central chondrosarcomas predominate in some groups (JAFFE) and peripheral in others (O'NEAL & ACKERMAN).

Table 1

Location of tumor in surgically treated and untreated patients

Site	Treated			'Untreated'			Total
	Central	Peripheral	Unknown	Central	Peripheral	Unknown	
Acetabulum	2	1	—	1	—	—	4
Ilium	—	3	—	4	2	1	10
Tibia	1	—	—	—	—	—	1
Femur	5	1	—	3	1	—	10
Humerus	—	—	—	1	1	—	2
Scapula	1	—	1	—	—	—	2
Hand	1	1	—	—	—	—	2
Sternum	—	—	—	1	—	—	1
Pubis	—	1	—	—	—	1	2
Sacrum	—	1	—	—	—	—	1
Ribs	—	1	2	—	—	—	3
Vertebra	—	—	1	—	—	—	1
Total	10	9	4	10	4	2	39

The major signs and symptoms may be seen in Table 2. It may be noted that 24 of the patients complained of pain at some period. Frequently the pain was not severe or persistent but occasionally patients had pain that gradually became severe enough to be incapacitating. All but three of the patients had evidence of a mass or swelling in the region of the tumor; among the peripheral chondrosarcomas a mass was frequently the only symptom. That chondrosarcoma has a rather long clinical evolution is well known. (DAHLIN & HENDERSON, JAFFE, O'NEAL & ACKERMAN, and LICHTENSTEIN.) Patients may have noted a slowly enlarging mass or pain for years before medical attention is sought. The dating of the onset of symptoms was often inexact. Two of the patients' tumors were discovered incidentally, one during an injection and one during puerperium. The duration of symptoms prior to diagnosis was approximately the same for patients having central and peripheral chondrosarcoma.

Table 2

Signs and symptoms in the material classified according to site

	Central lesion	Peripheral lesion	Unknown site	Total of cases
Pain	16	4	4	24
Stiffness or pain on movement	7	—	2	9
Muscle atrophy	5	—	—	5
Tumor or swelling	18	12	6	36
Tenderness	3	—	2	5
Fluid in joint	1	—	—	7
Local temperature	1	—	1	2

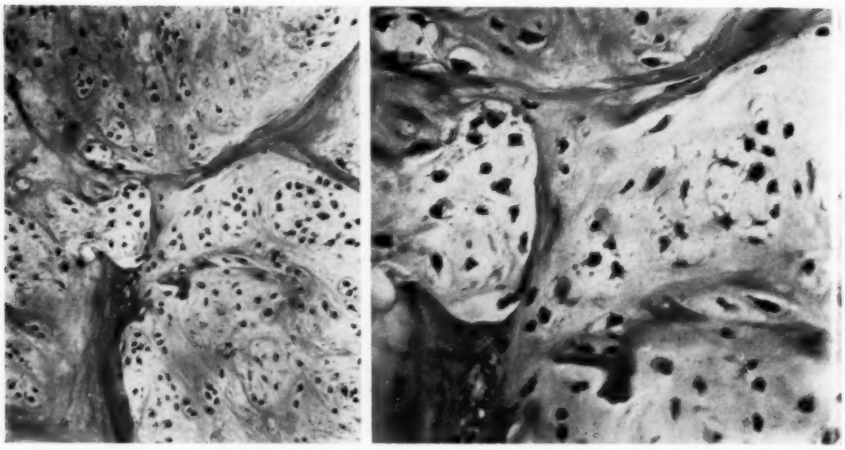

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Fig. 2. Chondrosarcoma grade I of vertebra. Plump nuclei and occasional binucleate cells. Three recurrent tumors curetted. Irradiation therapy given. Patient alive after 15 years. van Gieson. a) × 90 and b) × 220.

Pathology. The malignant component of chondrosarcoma is cartilaginous whereas, in the chondroblastic type of osteosarcoma, malignant cartilage is associated with malignant bone and osteoid and a malignant stroma. These two conditions can ordinarily be separated microscopically. The problem revolves around defining criteria for the well differentiated chondrosarcoma. It is among the well differentiated lesions that an erroneous diagnosis is most common. The criteria used are those described by LICHTENSTEIN and JAFFE. The validity of the criteria has been supported by others, notably O'NEAL & ACKERMAN and DAHLIN & HENDERSON. The criteria are (1) many cells with plump nuclei, (2) more than an occasional cell with two such nuclei, (3) giant cartilage cells with large single or multiple nuclei or with clumped chromatin. Variations as to quantity of the cell alterations plus the presence or absence of calcification and enchondral ossification form the basis for grading chondrosarcomas (O'NEAL & ACKERMAN (Figs 2, 3, 4) (Table 3)).

Our findings when using the above mentioned criteria confirm those of other observers, i. e. that the well differentiated chondromatous tumors with the nuclear aberrations described are indeed malignant neoplasms capable of invasion, destruction, recurrence and of distant metastases. It is true that the number of patients with known metastases in our group is small, 8 out of 39, but two of the cases with metastases had well differentiated chondrosarcoma (grade I). Seven of the 19 grade I chondrosarcomas had recurrent

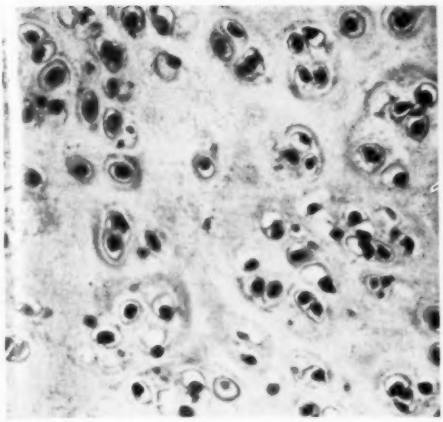

Fig. 3

Fig. 4

Fig. 3. Central chondrosarcoma grade II of femur. Somewhat more cellular than grade I. Plump nuclei, binucleate cells present. Treated by irradiation only. Patient died two years after biopsy confirmation of tumor. Hematoxylin and eosin. × 220.

Fig. 4. Chondrosarcoma grade III of ilium. Bizarre nuclear and cellular pattern. Irradiation therapy after biopsy. Patient died after two years. Hematoxylin and eosin. × 220.

Fig. 5. Embolus of chondrosarcoma grade III in artery. Primary tumor centrally in femur in a girl aged 16. Disarticulation of hip after biopsy. Died three and a half years later with pulmonary metastases and numerous arterial emboli of chondrosarcoma. Hematoxylin and eosin. × 35.

Fig. 5

lesions; this is not necessarily a measure of the potential of the tumor but possibly a reflection of the adequacy of removal. However, it does seem to indicate some vigor on the part of the tumor.

The grading of our cases was based upon the criteria of O'NEAL & ACKERMAN (Table 3). Since 16 of the patients had biopsies only, the material for grading was not always generous, and consequently the grading in these cases may not reveal the potential of the entire tumor. Nineteen of the cases (50 %)

Fig. 6. Chondrosarcoma grade I filling out almost the entire diaphysis of femur in a woman aged 44. Lobulated destruction of cortical layer from within and expansion of bone in places. Typical spotty calcification centrally in tumor tissue.

were regarded as grade I, fourteen (37 %) were grade II, and five (13 %) were grade III. The distribution of the grades is similar to that reported by DAHLIN & HENDERSON.

The best biopsy provides enough viable tumor tissue upon which a helpful opinion can be rendered. This usually means a carefully performed, generous incisional biopsy. Among our patients there were 24 who had biopsy prior to therapy; 8 of these were needle biopsies. It is possible to establish a specific diagnosis from a study of needle biopsies of cartilaginous tumors and even in the small fragments of tissue the criteria enumerated for malignancy could be found. Small portions of richly cellular cartilage with many atypical nuclei were occasionally obtained. As with any small biopsy, variation in the pattern of a tumor may often result in an uncertain or benign labelling of malignant growths. It must be emphasized that the clinical findings and the roentgenogram are important adjuncts to the diagnosis even when larger fragments of tissue are obtained.

Microscopic study of the recurrent lesions failed to reveal any increase in the grade of malignancy as compared to the original tumor. The survival time of the patients with and without recurrences is the same, an average after the first tissue diagnosis of 8.3 years for those with recurrences and 8.5 years for those without recurrences. This would suggest that in our small group of cases the recurrent lesions had not increased in malignancy and would correlate with our findings by microscopy.

Eight (21 %) of the patients had distant metastases, demonstrated either microscopically or macroscopically. In all except one of the cases the metastases were in the lungs; the exception was lymph node metastases in the case of a chondrosarcoma of the left humerus. In one case several arterial emboli of tumor tissue were produced by the pulmonary metastases (Fig. 5). In addition to the eight cases with metastases, one case had direct invasion of the vagina from a chondrosarcoma of the ilium. This occurred in a 64-year-old woman who died 3 months after diagnosis. Removal of the tumor was not attempted.

Fig. 7. Manubrium of sternum expanded by chondrosarcoma in a man, 84 years old.

Fig. 8. Chondrosarcoma grade II in distal metaphysis of femur in man of 28. Small spotty calcifications indicate nature of process; its unusual appearance somewhat suggestive of aneurysmal bone cyst.

Five of the patients with metastases had central chondrosarcoma, two peripheral and one of unknown classification. Four of the patients had received no therapy other than irradiation, two had been treated primarily by amputation, and two had amputation for locally recurrent tumor.

Roentgenographic findings. Spotty calcification of the type seen in cartilaginous tumors was observed in 22 of the 39 cases (Fig. 6). In 15 of the 22 cases the calcification was so abundant and typical that one could say with a high degree of certainty that the tumor was cartilaginous. Periosteal bone formation was noted in 8 of the cases. Twenty-one cases in all had roentgen evidence of bone destruction, the areas of destruction being plainly lobulated in 10 cases (Fig. 6). The bone was expanded around seven of the tumors (two of the femur, one of the sternum, Fig. 7, one of the acromion and three of the pelvis). The greatest diameters of the tumors, measured from the first films of the tumor, varied greatly. The largest tumor was a central chondrosarcoma of the femur; this tumor measured 30 cm in length. The two smallest measured 2 cm

in their greatest diameter and were from the index finger and the acetabulum. The chondrosarcoma with the largest mass occurred in the ilium and measured 23 × 15 cm.

Evidence of a soft-tissue component was seen in 25 of the cases. The soft tissue tumor could often be detected because of the presence of calcification in a few cases the tumor was so large that it was readily seen roentgenographically, contrasting with the surrounding fat. In several cases scalloped calcifications outlined the soft-tissue component of the chondrosarcoma (Fig. 8). This was especially evident in some cases after roentgen treatment (Fig. 9).

Sclerosis of bone was observed in 10 cases. It was often difficult to determine whether the sclerosis occurred in the bone or was the result of superimposed calcific foci in the tumor.

Roentgenographically 13 of the cases were so typical of chondrosarcoma that one could make the diagnosis with certainty. Two of the cases occurred in the femoral diaphysis (Fig. 6), two involved ribs, and the remainder the pelvis or upper femur. Histologically, 10 of these typical cases were considered grade I and 3 as grade II. Thus those most roentgenographically characteristic were very well or moderately well differentiated. The roentgenograms of the poorly differentiated chondrosarcoma were generally less typical of that tumor.

The tumor was not noticed on the first roentgen examination in four of our cases. All of these lesions were small. Three of the tumors were located in the acetabulum (Fig. 10) and the fourth involved a femoral condyle (Fig. 11).

Of the 26 cases in which the roentgenographic appearances were considered as being atypical of chondrosarcoma, 12 presented a picture that suggested a malignant tumor of an undetermined type. In 9 of these 26 cases some spotty calcifications indicated the possibility of a cartilaginous tumor. Approximately a third of all chondrosarcomas seem to have quite typical roentgenographic appearances.

Treatment. For all practical purposes the treatment of chondrosarcoma is surgical. In our experience and in that of others irradiation therapy has proved to be only palliative (DAHLIN & HENDERSON, JAFFE, HAGGART et coll.). As a general principle in surgical management, biopsy should precede radical treatment. With a confirmed diagnosis the proper surgical procedure, based upon location of the lesion in relation to the part of the body, physical state of the patient and microscopic appearances of the tumor, may be undertaken. The procedure of choice is one that will entirely encompass the lesion. In some instances this may mean hemipelvectomy or amputation but in other cases local resection may suffice. A peripheral chondrosarcoma of the metaphysis of the femur, for example, may very well be treated by local resection. Slow evolution of the tumor and a tendency to local recurrence before metastases appear make

a b

Fig. 9. Chondrosarcoma grade I in wing of ilium in man aged 41. Effect of irradiation. a) Recurrence of tumor after two resections 8 and 4 years earlier. Postoperative defect in ilium. Spotty calcification in recurrent tumor tissue. b) Two years later, after irradiation, calcification of tumor tissue.

local resection possible in many such cases. Chondrosarcoma of the pelvis on the other hand is difficult to treat by local resection as it is often impossible adequately to remove the entire tumor, and eventually distant metastases may occur. The nature of the condition often gives the surgeon a second or a third chance (LEWIS & PELTIER). Ordinarily hemipelvectomy is the most successful method of treating chondrosarcomas of the pelvic bones. Of the malignant diseases successfully treated by hemipelvectomy chondrosarcoma is in fact in the forefront (COLEY et coll., TAYLOR & ROGERS, LEWIS & BICKEL).

Twenty-three of our patients were subjected to some form of surgical treatment; eight patients had amputation, twelve patients underwent local resection and 3 had local resection followed by amputation. Fifteen of the patients had either pre-operative or postoperative irradiation or both. Benefits, if any, from the irradiation are obscure except as pertain to palliation. Doses varied from 1 600 r air dose to 13 600 r air dose; the treatments were often given in interrupted series. One patient with a grade I peripheral chondrosarcoma of the ilium developed an undifferentiated sarcoma at the site of irradiation some 13 years after initial excision and 5 years after irradiation therapy, a total dose of 12 300 r in four spaced doses having been given. Three recurrent tumors, all chondrosarcoma, had been removed 13 years, 9 years and 5 years

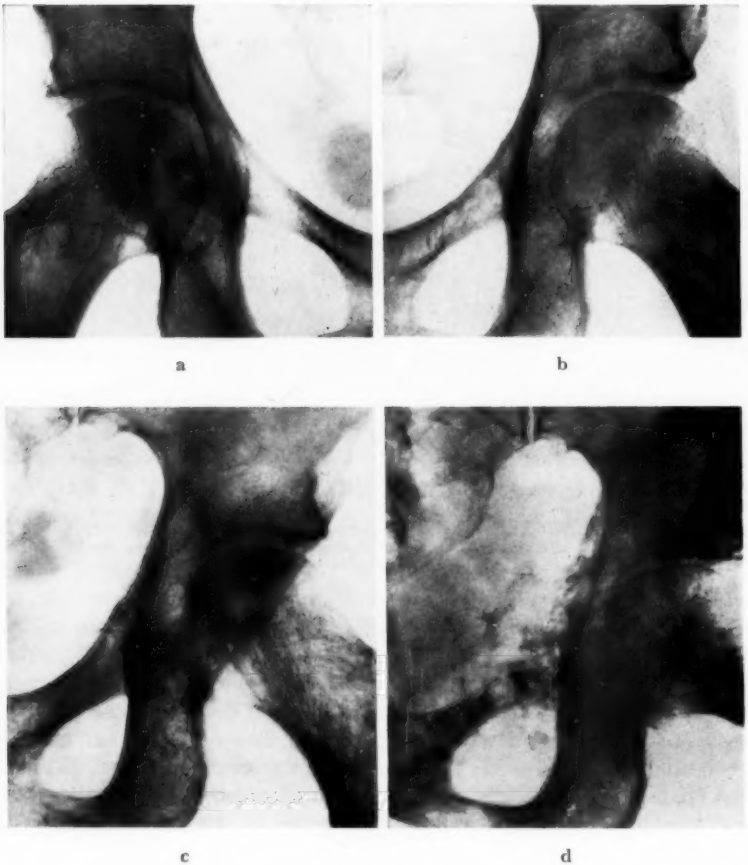

Fig. 10. Chondrosarcoma grade I in acetabular region in woman, aged 61. a) Healthy side. b) Small destruction medially in acetabulum. c) After one and a half years slow growth, obvious roentgenographic changes. Rarefaction, 3—4 cm large, with destruction of cortical layer. d) Another one and a half years later. Large tumor growing into pelvis with destruction of pubic bone.

before the undifferentiated sarcoma appeared. It is possible that the sarcoma represented an undifferentiated form of chondrosarcoma or an irradiation-induced sarcoma.

The success of a mode of therapy for a malignant neoplasm may be judged not only on long term survival but on recurrences. Of our 15 patients treated initially by local resection (curettage not included), 11 (73 %) had one or

Fig. 11. Small chondrosarcoma grade II of lateral femoral condyle in man, aged 32. Poorly delimited destruction and slight periosteal reaction (arrows).

more local recurrences. Eight patients were treated primarily by amputation; two of these had local recurrence of the tumor. The high frequency of recurrent chondrosarcoma would seem to indicate that the potential of the tumor was not appreciated and the field of excision was consequently unduly conservative. The recurrence in itself, as already indicated, does not necessarily hasten the death of the patient, but often the recurrent tumor becomes more and more inaccessible until removal is impossible. In terms of 5 years' and 10 years' survivals the figures for those patients having recurrent chondrosarcoma are nearly the same as for patients without recurrence (61 % 5 years' survival and 31 % 10 years' survival with recurrent tumor; 56 % 5 years' survival and 44 % 10 years' survival without recurrence).

The group of essentially untreated chondrosarcomas is of special interest. From a study of these cases it has become apparent that cartilaginous tumors of long and flat bones, judged benign from the insidious progress or lack of microscopic evidence of frank malignancy, are often in fact malignant, as determined from the course. The peripheral lesions of this group are similar

Table 3

Classification of the material in histologic groups, based upon the criteria of O'NEAL & ACKERMAN *indicated by the roman numerals*

Low grade (I)	Moderately malignant (II)	Highly malignant (III)
Occasionally very plump nuclei or general plumping of many nuclei	Many plump nuclei	Great variation of nuclear size and many very plump nuclei
Few double nuclei	Frequent plump double nuclei	Many double nuclei
No multinucleated giant cells	None to rare multinucleated giant cells	Occasional to frequent multinucleated giant cells
Enchondral osteogenesis often irregular	Enchondral osteogenesis bizarre and disorganized	No enchondral osteogenesis
Calcification frequent	Occasional but slight degree of calcification	No calcification

clinically and roentgenographically to those that have been classified as giant osteochondromas or 'extensive osteochondroma' (COLEY). All sixteen patients had a biopsy, from the time of which until death the average length of life was 1.8 years with a time span of 3 months to 14 years. If the one survivor is subtracted, the time range of survival is 3 months to 4 years. Survival from onset of symptoms until death, with one exception, averaged 4.2 years with a span of 10 months to 14.5 years. For comparison the survival times for the patients who had surgical treatment averaged 8.6 years from biopsy to the end of the follow-up period and 10.5 years from the beginning of symptoms to the end of the follow-up period. Four of the 16 cases had known metastases and one had invasion of the vagina. As no postmortem examination was performed in most of those patients who died, information as to the actual numbers with metastatic sarcoma or of the extent of the primary tumor, was not obtained.

The reason for not giving treatment other than irradiation therapy to these patients was not always clear from the notes. Refusal of surgery by the patient, poor physical condition of the patient, reluctance on the part of the pathologist to diagnose chondrosarcoma, the presence of pulmonary metastases, were all reasons for lack of surgical intervention. Age was possibly a factor in relation to the physical condition as in this group the average age was 52.5 years, whereas for the treated patients the average age was 41.6 years. The location of the lesions in the two groups was similar (Table 1); however, more than half of the 'untreated' cases were central types although less than half were central in the surgically treated group. The size of the tumor, as determined roentgenographically, did not seem likely to have influenced the type of therapy in most cases. In the two groups the average size was the same, 9.2 cm in diameter. Histologically, as far as grade of malignancy was concerned, 10 (62 %) were grade I, 3 (19 %) grade II and 3 (19 %) grade III.

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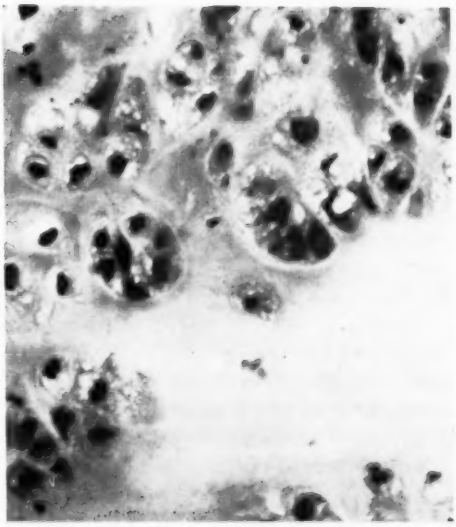

c

Fig. 12. Central chondrosarcoma grade I of humerus in man, aged 52. Treated by curettage biopsy followed by irradiation. Alive 15 years after biopsy.

a) Lobulated, fairly well delimited destruction in head of humerus.

b) Irregular bone sclerosis in tumor region three years after treatment.

c) Photomicrograph. Hematoxylin and eosin. × 280.

This compared with 50 % grade I, 37 % grade II and 13 % grade III for the entire group.

All of the 16 patients classified as 'untreated' received irradiation therapy. There was no planned program of irradiation treatment of chondrosarcoma. The patients received from 1 200 r to 18 600 r air dose in the tumor area. Seven of the patients noted no change in symptoms, usually pain, or in the size of the tumor following irradiation. The other patients felt less to no pain after therapy, and three were aware of a decrease in the size of the tumor. All of the palliative effects were temporary except in the one patient who survived 14 years after irradiation; this was a 52-year-old man with pain in his right shoulder. Biopsy of the lesion was performed by curettage and several soft cartilaginous fragments were examined and alterations suggestive of chondrosarcoma were noted. The patient received 2 000 r to a posterior field and 2 000 r to an anterior field over the tumor, and three years later additional irradiation was administered to bring the total dose to 5 500 r to the anterior field and 5 100 r to the posterior field. It is not certain whether the curettage, which yielded a fairly small amount of tissue, was sufficient to have removed the lesion. Possibly the combination of the curettage and the irradiation were equally or together effective in producing a 14 years' survival (Fig. 12).

Prognosis. Because of the long course of many chondrosarcomas before and after treatment, and even with inadequate treatment, the standard of 5 years' survival has less meaning than, for example, in osteosarcoma. Figures for 5 and 10 years' survival have been infrequently published. GESCHICKTER & COPELAND reported a 5 years' survival rate after operative treatment of 44 % (38 patients alive and well out of 86).

All of our patients were followed for a minimum of 5 years or until death. The overall 5 years' survival is 38 % (15 patients who lived 5 years). The 10 years' survival is 23 % (9 patients lived 10 years or more). If the three patients who are not as yet eligible for 10 years' survival are not included to calculate the 10 years' survival, the figure is 25 %. The follow-up period for these calculations began with the first biopsy or resection. Basing the survival on the entire life history of the chondrosarcoma, the 5 years' survival for our patients is 59 % (23 lived 5 years or more). The 10 years' survival is 26.3 % (10 lived 10 years or more). Of the patients who died, 26 were said to have died with tumor and 5 died without clinical or autopsy evidence of chondrosarcoma. One of the 8 patients alive today has persistent chondrosarcoma; the other seven patients are clinically free from tumor.

The benefit of surgical therapy, even though not always adequate, is evident from the 5 and 10 years' survival figures for our group of 'untreated' cases. Among our patients receiving only irradiation therapy after biopsy, one survived 5 years; the same patient has survived more than 10 years. Thus the 5 and 10 years' survival is 6.2 %. Of the 23 patients treated surgically, 14 (60.9 %),

survived 5 years or more, postoperatively. Eight patients lived 10 years or more (34.8 %).

From the aspect of anatomic location, peripheral or central in bone, the patients having chondrosarcomas classified as peripheral have a better 5 and 10 years' survival rate than those with central chondrosarcoma. The comparative figures are: peripheral 5 years' survival 53.8 %, and 10 years' survival 30.7 %, the central 5 years' survival is 30 %, and the 10 years' survival 20 %. Among the tumors of unknown classification there was one case which survived 7 years and another 15 years. Survival related to chondrosarcoma of the axial skeleton (including pelvis, vertebra and ribs), or bones of the limbs, shows that the survival percentage is better in cases of chondrosarcoma of the extremities. This would be expected. The 5 years' survival for chondrosarcoma of the extremities is 46.6 % (7/15); the 10 years' survival is 33.3 % (5/15). For chondrosarcoma of the axial skeleton the 5 years' survival is 33.3 % (8 survivors among 24) and the 10 years' survival 16.6 %.

Related to the histologic grade of the tumor the results are reverse of what would be expected, *i. e.* the survival was better for grade II as opposed to grade I. The 5 years' results were 42 % for grade I and 47 % for grade II. The 10 years' survival percentages were 31 % and 36 % respectively. None of the 5 cases with grade III chondrosarcoma survived as long as 5 years.

Conclusions

The diagnosis of cartilaginous tumors by microscopy is often difficult and requires considerable experience. It is, however, most important if treatment is to be adequate and satisfactory. Our 16 patients, who were essentially untreated except for irradiation therapy, illustrate well the outcome of chondrosarcoma under such circumstances. The 5 and 10 years' survival figures are poor compared to those patients who had some form of surgical therapy.

In terms of length of life, even poorly performed local resections of chondrosarcomas give good results in the face of local recurrences. Well performed resections or amputations with a low recurrence rate do not, as our figures indicate, give much better 5 and 10 years' survival rates. Other factors also influenced prognosis in our cases. If the lesion was located in a bone of an extremity as opposed to in bones of the axial skeleton the prognosis was more favorable in terms of percentage of 5 and 10 years' survival. Similarly peripheral chondrosarcomas have a better survival rate than central chondrosarcomas. The histologic grade of malignancy was of particular prognostic significance, whereas none of the cases with grade III chondrosarcoma survived 5 years.

Our study supports previous observations that chondrosarcoma is a slowly progressive tumor both before and after diagnosis. However, even those that appear to be pathologically and roentgenologically benign are capable of local recurrence and of distant metastases. Surgical treatment, suited to the location of the lesion, is the procedure of choice. Except in one case radiation

therapy served only as a temporary palliative of local symptoms. In a few cases the size of the tumor appeared to regress under irradiation.

The overall 5 years' survival rate was 38 % and 10 years' survival 23 %.

SUMMARY

Primary chondrosarcoma of bone was studied in a material of 39 cases. Sixteen of the cases were treated only with irradiation and the 5 year survival rate was 6.2 %. Twenty-three patients had either local resection, amputation, or both, with a survival rate of 60.9 % for 5 years and 34.8 % for 10 years. The overall 5 years' survival rate for the 39 patients was 38 % and the 10 years' rate 23 %.

ZUSAMMENFASSUNG

Das primäre Chondrosarkom des Skeletts wurde an einem Material von 39 Fällen studiert. Sechzehn der Fälle wurden nur strahlenbehandelt und 6.2 % zeigten eine 5-jährige Überlebenszeit. Dreiundzwanzig Fälle wurden entweder lokal reseziert, amputiert oder beiden Eingriffen unterzogen und 60.9 % von diesen zeigten eine 5-jährige und 34.8 % eine 10-jährige Überlebenszeit. Von allen 39 Patienten lebten 38 % nach 5 Jahren und 23 % nach 10 Jahren.

RÉSUMÉ

Les auteurs étudient le chondrosarcome primitif de l'os sur une série de 39 cas. Seize de ces cas ont été traités uniquement par les radiations, avec un taux de survie de 5 ans de 6.2 %. Ving-trois malades ont subi soit une résection locale, soit une amputation, soit les deux, avec un taux de survie de 60.9 % à 5 ans et de 34.8 % à 10 ans. Le taux de survie de 5 ans de l'ensemble des 39 malades fut de 38 %, et de 23 % 10 ans.

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ROENTGEN EXAMINATION OF THE INFERIOR VENA CAVA IN CHRONIC HEPATIC DISEASE

by

OLAF PETERSEN, NIELS TYGSTRUP and KJELD WINKLER

Pressure measurements in the central veins in cirrhosis of the liver have shown that a pressure gradient exists between the abdominal and thoracic part of the inferior vena cava in about one third of cases (WINKLER, TYGSTRUP & HANSEN 1960). The gradient usually occurred centrally to the outlet of the hepatic veins at the level of or just below the diaphragm. The present study was carried out in order to assess if this gradient could be attributed to narrowing of the infra-diaphragmatic part of the inferior vena cava.

Roentgen examination of the inferior vena cava with injection of contrast media has been widely used, particularly for demonstration of retroperitoneal tumours (dos SANTOS 1935, O'LOUGHLIN 1947, OLIVIER 1951, HELANDER & LINDBOM 1956, 1959), but generally only the caudal part of the vein, i. e. the part below the renal veins, has been examined. There is little information about the configuration of the upper course of the inferior vena cava. VIALLET et coll. (1957) have described a more or less marked compression of the intrahepatic part of the vein in Algerian children with hepato-splenomegaly, and a paper by FARIÑAS (1947) contains an illustration showing a constriction of the vein in a patient with hepatic cirrhosis.

Submitted for publication 27 June 1960.

Table

Survey of material

No.	Age	Sex	Clinical condition	Smallest area of inf. vena cava as a percentage of supradiaphragmatic area	Pressures in mm Hg	
					Right atrium	Inf. vena cava
1	16	f	Normal	82	5	6
2	17	m	Normal	49	3	5
3	50	m	Bronchial asthma	61	3	4
4	17	f	Normal	25	4	5
5	51	m	Chronic bronchitis	10	5	7
6	57	f	Cirrhosis	20	3	5
7	54	m	Cirrhosis	24	10	16
8	53	f	Cirrhosis	10	5	6
9	55	m	Fatty liver	9	8	13
10	63	m	Cirrhosis	37	4	5

Material and Methods

The diagnoses of the cases are given in the Table above. Cases 1 to 5 had no clinically demonstrable hepatic disease, and in Cases 6 to 10 the diagnoses were confirmed by liver biopsy. In the cases of cirrhosis the condition was at an advanced stage, but ascites, when present, did not noticeably distend the abdominal wall. Case 9 (with fatty infiltration of the liver due to chronic alcoholism) had a large liver and moderately abnormal liver function tests.

The patients were premedicated by 200 mg of phenobarbitone; apart from this no anaesthesia was given. The examination was performed with the patients supine. A Lehman catheter was introduced via an antecubital vein into the inferior vena cava with the tip at the level of Th 12, i. e. below the outlet of the hepatic veins, and 33 to 40 ml Urografin® 76 % were injected with an automatic pump (Gidlund) during 3 seconds. Five exposures in the antero-posterior and lateral planes were made at intervals of one second. The patients were instructed to stop breathing during the exposures (without Valsalva manoeuvre). The injection was generally accompanied by a momentary burning but not painful sensation in the upper abdomen; apart from this no side-reaction was observed. The pressure measurements listed in the table were performed with the Tybjærg Hansen condenser manometer as previously described (WINKLER et coll. 1960).

Results

The inferior vena cava from the level of the renal veins to the right atrium is clearly outlined with the technique employed. This is largely due to the fact that the contrast medium is injected against the blood flow in the vein so that the contrast medium and blood are thoroughly mixed. No backflow of the medium to the hepatic veins was observed; on the contrary, dilution of the contrast medium by hepatic venous blood was frequent. Care must be taken

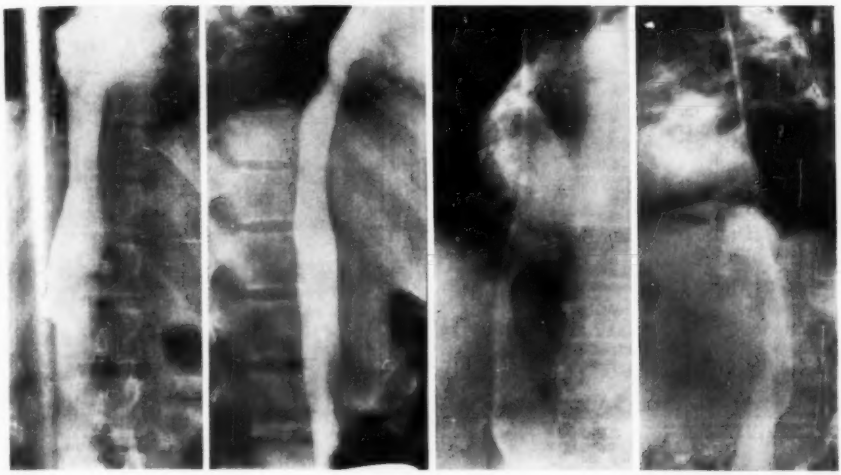

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Fig. 1. Normal case. a) A.p. Gradual diminution of the lumen of the inferior vena cava from the renal veins to the diaphragm. The lumen of the supradiaphragmatic part of the vein again increases and remains constant until the vein enters the right atrium. b) Lateral. Only small alterations in size are seen. There is no reflux of contrast medium into the hepatic veins.

a b

Fig. 2. Hepatic cirrhosis. a) A.p. Considerable decrease in size of the vena cava at the level of the diaphragm. b) Lateral. The constriction is less marked. The contours of the vein just below the diaphragm are not sharp anteriorly due to mixing with blood free of contrast medium, from the hepatic veins.

not to mistake this phenomenon for a narrowing of the lumen. Contraction of the inferior vena cava during the atrial systole, as described by KJELLBERG & OLSSON (1954), could not be demonstrated.

In the subjects with a normal liver the diameter of the inferior vena cava in the antero-posterior projection gradually decreases from the level of the renal veins to the diaphragm, above which it again increases to remain constant to the point where the vein enters the right atrium (Fig. 1a). The same configuration, but generally less evident, could be seen in the lateral projection (Fig. 1b). The degree of narrowing varied greatly in the subjects studied. In the patients with disease of the liver this narrowing appeared to be accentuated; in some of the cases it was most clearly seen in the a.p. view (Fig. 2) and in others in the lateral projection (Fig. 3).

The transverse sectional area of the inferior vena cava at different levels was calculated from the diameters in the a.p. and lateral projections, presuming the transverse section to be elliptical when the diameters were different. In order to compare the degree of narrowing from case to case, the sectional area of the abdominal part of the inferior vena cava was expressed as a percentage of the

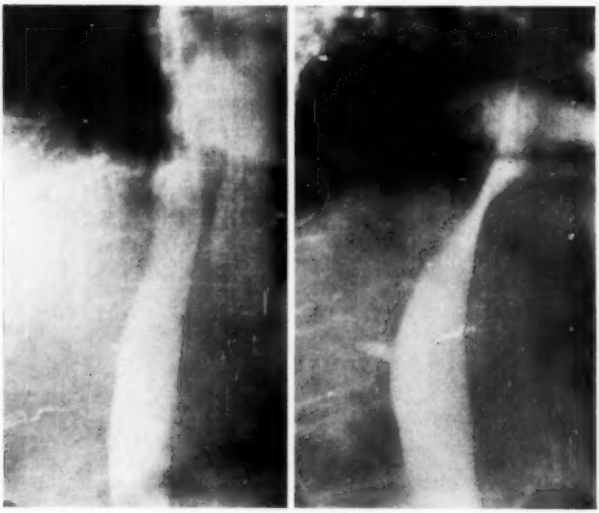

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Fig. 3. Hepatic cirrhosis. a) A.p. Only an insignificant constriction of the inferior vena cava is evident. b) Lateral. A marked diminution in size near the diaphragm is now apparent.

area of the thoracic part (the Table and Fig. 4). The Table shows that the individual variation is considerable, although, if the average values of the normal subject and of those with hepatic disease are compared, a true difference can be demonstrated. The smallest area as a percentage of the area of the thoracic part was in the cases with a normal liver 36 % and in the cases of hepatic disease 18 %.

Discussion

Interpretation of the results is difficult because no definite limit between the narrowing of the sub-diaphragmatic part of the inferior vena cava in cases with and without hepatic disease could be demonstrated. However, as this narrowing is more constant and generally more marked in the cases of liver disease, it appears justifiable to consider it at least contributory to the abdomino-thoracic venous pressure gradient frequently observed in this condition.

The etiology of the narrowing is not elucidated by this study. It may equally well be due to compression of the intra- or retro-hepatic part of the vein, e. g. caused by regeneration nodules in the fossa venae cavae of the liver, and to

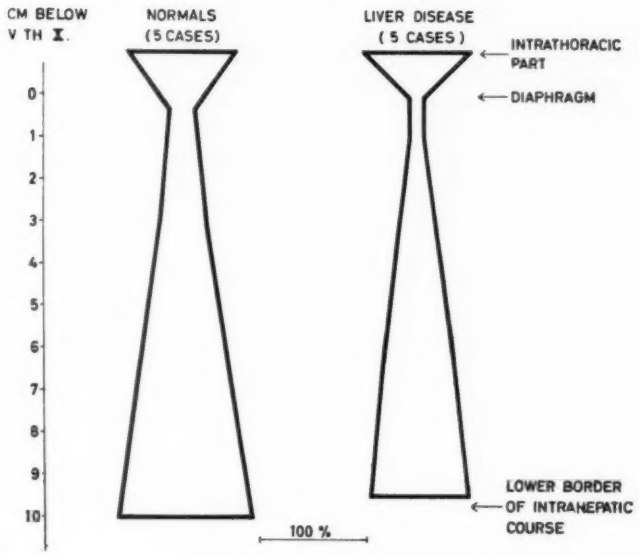

Fig. 4. Average horizontal cross section areas of the inferior vena cava in normal individuals and patients with liver disease.

increased intra-abdominal pressure, i. e. a 'functional stenosis'. In the present material ascites in sufficient amounts to cause increased pressure in the abdominal cavity was not present, and in our opinion the first-mentioned hypothesis seems to be the more acceptable. The material presented is too small to show whether there is a correlation between the pressure gradient and the narrowing, as shown by cavography with the present technique; for this purpose further standardization of the method and determination of the inferior caval blood flow would appear to be necessary.

The significance of increased pressure in the inferior vena cava in the pathogenesis of portal hypertension and ascites has been previously discussed (Winkler, Tygstrup & Hansen 1960).

SUMMARY

Angiographic examination of the inferior vena cava in 5 cases of chronic hepatic disease and 5 normal controls have shown that narrowing of the vein just below the diaphragm was more marked in the former group. This may be caused by pressure exerted by the diseased liver on the intra- or retro-hepatic part of the vein and may partly account for the increased abdomino-thoracic venous pressure gradient described in cases of cirrhosis.

ZUSAMMENFASSUNG

Angiographische Untersuchungen der Vena cava inferior in 5 Fällen mit chronischer Lebererkrankung und in 5 normalen Kontrollfällen haben gezeigt, dass eine Verengung der Vene unmittelbar unter dem Zwerchfell in der ersten Gruppe deutlicher markiert war. Dieses kann durch den Druck verursacht sein, der von der erkrankten Leber auf den intra- oder retrohepatischen Teil der Vene ausgeübt wird und kann teilweise den erhöhten abdominothorakalen venösen Druckgradient erklären, der in Fällen mit Zirrhose beschrieben wird.

RÉSUMÉ

L'examen angiographique de la veine cave inférieure dans 5 cas d'affection hépatique chronique et chez 5 témoins normaux a montré que le rétrécissement de la veine, juste au dessous du diaphragme, est plus marqué dans le premier groupe. Ceci peut être dû à la pression exercée par le foie pathologique sur la partie intra- ou rétro-hépatique de la veine et peut expliquer en partie l'augmentation du gradient de pression veineuse abdomino-thoracique constatée dans des cas de cirrhose.

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PARTIAL PERSISTENCE OF THE DUCTUS ARTERIOSUS

by

CARLOS QUIROGA

A small dimple in the endothelium of the pulmonary trunk at its division into right and left branches is frequently found in cardiovascular specimens and marks the attachment of the obliterated ligamentum arteriosum. A persistent patency of the ductus represents an aberration of the obliterating process, normally taking place in the postnatal period. A partial persistence of the ductus lumen with patency of its pulmonary end but with the aortic end obliterated is considered rare. GREIG et coll. (1954), have observed such patency in only one out of 148 adult cadavers in which the ductus area was examined. The case mentioned by KJELLBERG et coll. (1959) appears to be the only one in which this was demonstrated by angiocardiography.

It is the purpose of the present work to give an account of the frequency of this condition and its angiocardiographic appearances in a series of congenital heart lesions.

Twenty-five instances of a partially open ductus arteriosus were found in the angiocardiograms of 735 cases in which the pulmonary artery was contrast-filled in various congenital heart lesions. These figures correspond to an incidence of 3.45 %.

The distribution is shown in the Table. This demonstrates that the occurrence of a partially patent ductus was mainly associated with malformations causing some kind of obstruction to the outflow of the right ventricle. Thus, pulmonary valvular or infundibular stenosis, mostly in combination with a ventricular

Submitted for publication 3 August 1960.

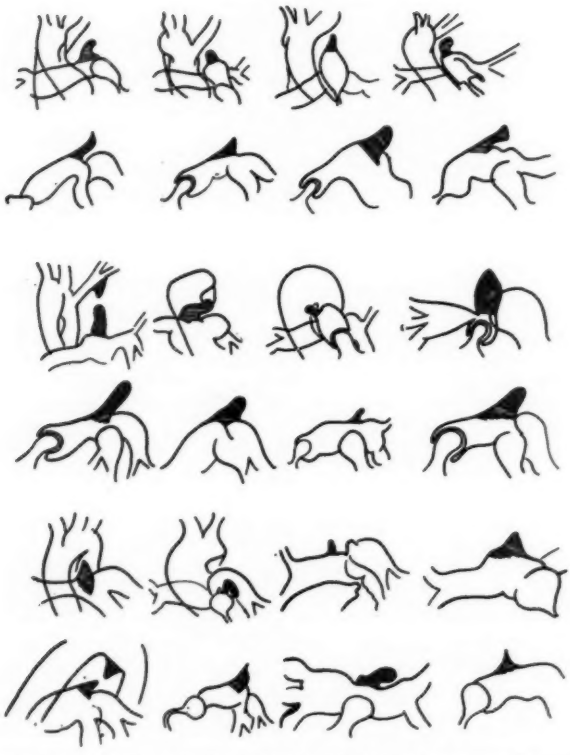

Fig. 1. Schematic drawings. Frontal and lateral representations of main angiocardiographic features of the great vessels in a selection of 13 cases with partially patent ductus arteriosus.

septal defect, was present in 22 of the 25 cases; in approximately half of the cases the existence of a right-sided aortic arch was noted. A reduction of the pulmonary vascularity was observed in 21 cases. A left-to-right shunt or a bidirectional shunt occurred in 19 cases, and 2 cases had a left-to-right shunt.

The various shapes of the ductus remnant and its relationships to adjacent vascular structures are demonstrated by the drawings in Fig. 1. As is evident from this figure, and from Figs 3 and 4, the patency of the ductus was confined to its pulmonary termination, and in no single case in the series reviewed to its aortic end. The ductus emerged from the superior and dorsal part of the pulmonary artery at the origin of the left main branch; only in one case did it communicate with the right pulmonary artery. The mouth of the ductus invariably was widely open and the patent portion of the ductus was as a rule

Table

Occurrence of partially patent ductus arteriosus in 25 cases of congenital heart lesions

	Number of cases	Right-sided aortic arch	Left-sided aortic arch	Associated anomalies			Shunt			Pulmonary circulation	
				V.S.D.	A.S.D.	Stenosis of pulm. branches	Right-to-left	Left-to-right	No shunt	Decreased	Normal
Pulmonary stenosis infundibular and/or valvular	22	13	9	19	2	1	19	2	1	19	3
Transposition of great vessels	2		2	1+2 vps						2	
Coarctation of the aorta	1		1						1		1
Total	25	13	12	21	2	1	19	2	2	21	4

vps = valvular pulmonary stenosis
V.S.D. = ventricular septal defect
A.S.D. = atrial septal defect

longest in cases with a right-sided aortic arch. The arrangement of the vascular structures in one case suggested that the ligamentous portion of the ductus was inserted into the left subclavian artery.

The ductus was identified in one case at autopsy (Fig. 5), and in two cases at operation at which it was sought. In one of these latter cases pulmonary valvotomy was performed by inserting the valvulotome through the ductus after dissecting it free from the pericardium; in the other case, the patent portion of the ductus was used for creating an anastomosis to the aorta in order to increase the blood flow to the lungs. It was observed in these three cases that the ductus in its extrapericardial portion had a ligamentous continuation that was inserted into the wall of the aortic arch.

Discussion

The present series demonstrates that a partially patent ductus can no longer be considered a rarity. The reason why such partial persistence of the ductus has apparently escaped the attention of the operator may be that the open part of the ductus may generally be expected to have an intrapericardial location and will thus not be readily detected. Our series does not offer any final indication as to the nature of the process causing the anatomic obliteration of the ductus to be confined to its pulmonary end. It can be stated only that its preponderant occurrence in conditions that are characterized by a reduced blood flow to the lungs suggests that the ductus may serve as a collateral in the

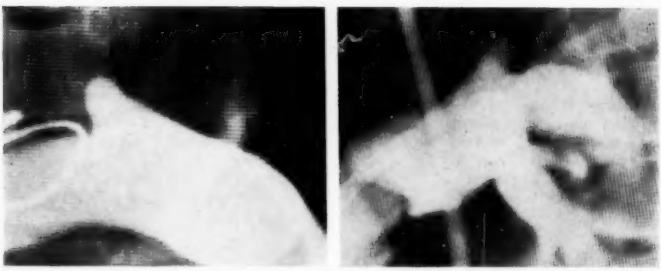

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Fig. 2. Girl, aged 7, operated on for tetralogy of Fallot. Right-sided aortic arch and a partially patent ductus arteriosus. a) Frontal view. b) Lateral view.

a b

Fig. 3. Boy, aged 19. Infundibular and valvular pulmonary stenosis, ventricular septal defect, right-to-left shunt, left-sided aortic arch and a partially patent ductus arteriosus. a) Frontal view. b) Lateral view.

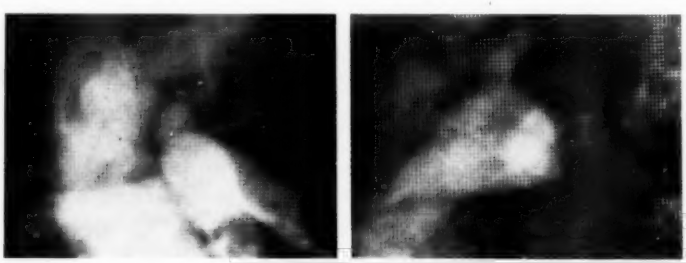

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Fig. 4. Girl, aged 3 years 6 months. Ventricular septal defect, infundibular stenosis, right-to-left shunt, right-sided aortic arch and a partially patent ductus arteriosus. a) Frontal view. b) Lateral view.

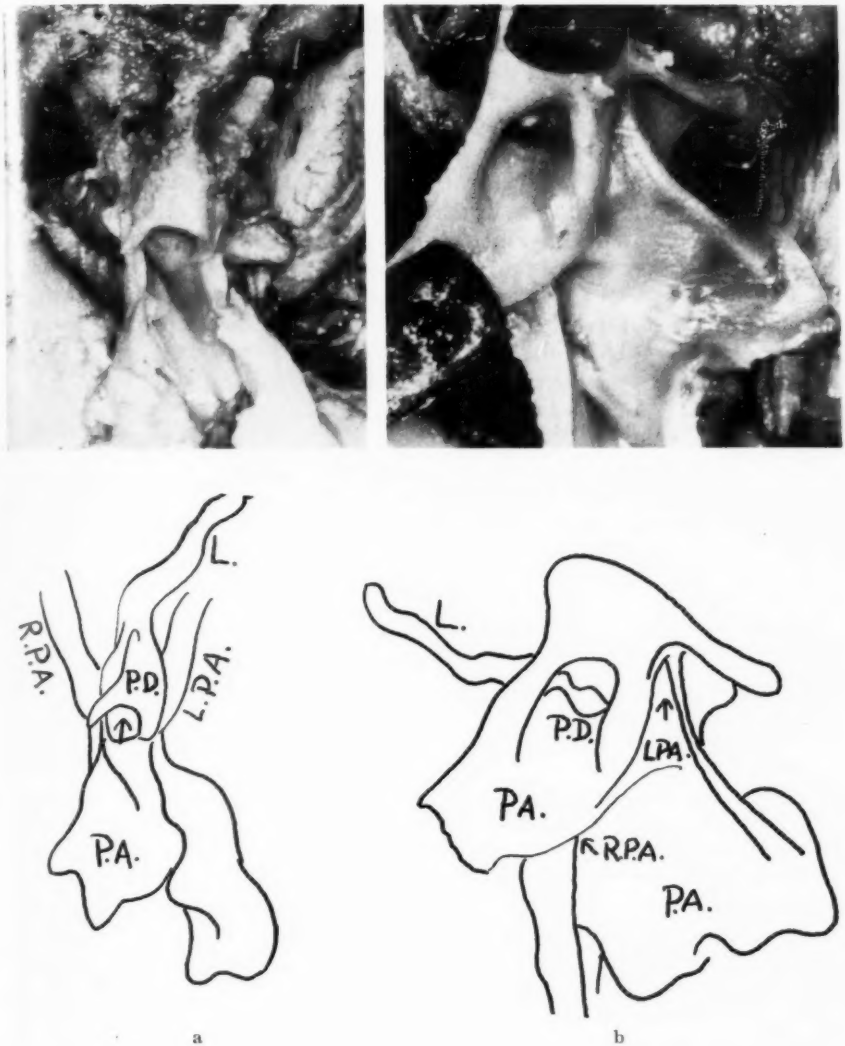

Fig. 5. Autopsy specimens from infant aged 6 months. a) Tetralogy of Fallot, right-sided aortic arch and anomaly of the systemic arteries. The partially patent ductus measured 6 mm in length and 2 mm in width. The pulmonary artery is cut along its anterior wall and the ligamentous portion is retracted by tweezers. Arrow points to the lumen of the ductus. b) The anterior wall of the pulmonary artery is retracted upwards so that the lumen of the remnant ductus is visible. P. D. — Partially patent ductus, — Ligamental portion, P. A. — Pulmonary artery trunk, L. P. A. — Left pulmonary artery, R. P. A. — Right pulmonary artery.

postnatal period, a function that becomes interrupted by the obliteration of the ductus at its aortic termination.

The widely open mouth in the pulmonary artery wall permitted the ductus easily to become contrast-filled during angiocardiography. The ductus invariably showed variations in size during the cardiac cycle and filled and emptied synchronously with the pulmonary artery. It was never found to harbour a thrombus and was never seen to be invaded by vegetations of bacterial endocarditis. In spite of the fact that in the cases combined with right-sided aortic arch the vascular structures must be expected to encircle the trachea no instance of compression of the latter was observed. The partially persistent ductus should therefore be regarded as a generally innocuous abnormality. That it may be a useful structure during heart operations was as mentioned above evident in two of our cases.

SUMMARY

An account is given of the angiocardiographic features, frequency, and distribution, of a partially patent ductus arteriosus in 25 cases of congenital malformations of the heart. In the majority of the cases the anomaly was associated with different types of outflow obstruction of the right ventricle, and in approximately half of the cases the aortic arch was right-sided.

ZUSAMMENFASSUNG

Das angiokardiographische Aussehen, die Häufigkeit und die Verteilung eines partiell offenstehenden Ductus arteriosus in 25 Fällen mit kongenitalen Missbildungen des Herzens werden berichtet. In der Mehrzahl der Fälle war die Anomalie mit verschiedenen Typen von Abflussverengungen des rechten Ventrikels verbunden und in ungefähr der Hälfte der Fälle lag der Aortenbogen rechtsseitig.

RÉSUMÉ

L'auteur décrit les caractères angiographiques, la fréquence, et la distribution de la persistance partielle du canal artériel dans 25 cas de malformations congénitales du cœur. Dans la majorité des cas, cette anomalie était associée à différents types d'obstacles à l'évacuation du ventricule droit, et, dans environ la moitié des cas, la crosse aortique était dextroposée.

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APPARATUS FOR CONTROLLED INFUSION OF SALINE IN ANGIOGRAPHY AND CONTRAST MEDIUM IN LYMPHOGRAPHY

by

B. CLEMENTZ and T. OLIN

The injection of contrast medium in angiography is made either through a needle inserted directly into a vessel or through a catheter. The vessel is generally punctured percutaneously and the cannula left in the vessel until the films have been processed and examined in case a second injection of contrast medium should be required. During the interval physiologic saline is usually injected at a slow rate to prevent clotting in the needle; the consequence of a clot being transmitted to the bloodstream might well prove disastrous, particularly in cerebral angiography. As an extra precaution some authors (CURTIS 1950—51) use a siliconized puncture needle, but this involves a risk, though a slight one, of fat embolism. Some radiologists (VERBRUGGHEN 1954) disconnect the needle from the syringe, rinse the lumen of the needle with heparin, and then introduce a suitable stilett; this technique minimizes the risk of coagulation but is apt to disturb the position of the needle.

Catheterization of the vessel by SELDINGER's technique entails the lumen of the catheter being filled for some time with a stainless steel guide; if this is not treated with heparin small clots will be produced from the ooze of

Submitted for publication 11 October 1960.

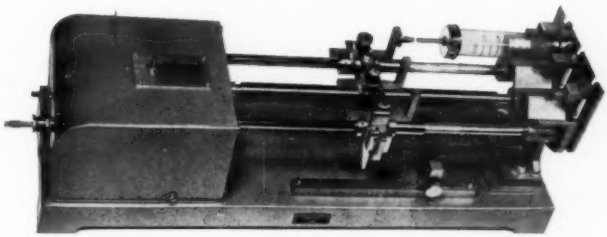
blood between the guide and the catheter and adhere to the former as it is withdrawn; the remainder will be washed out by the return flow of blood. Physiologic saline is then infused slowly through the catheter in the usual way before and after the injection of contrast medium. ÖDMAN, using a special three-ribbed-catheter, rinsed its lumen with heparin from time to time while the guide was still in position.

Saline is thus infused sometimes for a fairly long period during angiography to minimize the risk of coagulation in the needle or catheter. The rate of infusion must be low in order to avoid infusion of more fluid than is necessary. Latent cerebral edema, for example in brain tumour or after head injury, may become manifest during carotid angiography if the amount of normal saline administered is excessive. It is no good trying to avoid this by using Macrodex (Pharmacia) in place of saline, because in brain tumours the permeability of the capillary wall is often impaired, with the result that the dextran molecules escape into the cerebral tissue and thereby favour edema.

The saline is usually infused manually with an ordinary syringe. The disadvantage of this method is that it is time-consuming and must be applied by a skilled operator; in addition, it is often difficult to inject at an even and low rate. A flask of the type used for intravenous drip may also be used. In arteriography of cases with arterial hypertension the flask must be placed 4 meter above the patient, which in practice means that the examination room must be at least 5 meter in height. The tubing is also long and unwieldy. We have tried this arrangement in vertebral angiography in children, with injection of the contrast medium through a catheter, but have not found it practical. Another method, used by RADNER and others, for arterial catheterization is to infuse saline under pressure from a bottle such as used for blood transfusions. The disadvantage of this method is the risk of air embolism, and accidents with this type of transfusion and infusion have occurred. The method requires skilled assistants and may even then be difficult to perform in the semi-darkness often necessary for catheterization.

Since none of the above methods have been found very satisfactory, an automatic infusion apparatus has been adopted. This is a type that has been used at the Institute of Physiology for the past 20 years for infusing various fluids into the bloodstream of experimental animals.

The apparatus shown in the accompanying photograph has been constructed by one of us (B. C.) and consists of three main parts: a syringe holder, a carrier with thrust rods, and a motor complete with gear box. The holder can accommodate three syringes of 1 to 100 ml capacity which are locked in position by simple devices. The carrier has two slides running on guides and driven by a long screw, the thread of which drives a half-nut fastened to the lower surface of the carrier by an articulated arm. This arm is spring-loaded and engages by means of a latch the thread of the half-nut with the thread of the screw. Application of pressure against the latch will disengage



Apparatus for controlled infusions of saline and contrast media.

the half-nut from the screw so that the carrier can be brought into any desired position. This uncoupling occurs also when the latch makes contact with an adjustable stop, thus preventing syringe damage when the plunger comes near to the bottom of its travel. The carrier is not pressed directly against the plunger of the syringe but the force is transmitted by means of one of the adjustable thrust rods, one being used for each syringe. The power from the governor-controlled electric motor is transmitted to the screw by a 10-speed gear. The governor permits fine adjustment between the gears, and by means of this arrangement the rate of the thrust rod can be continuously varied between 0.15 mm/min and 32.6 mm/min.

We have used this machine for more than 3 years as a routine in angiography and found it to be both simple and reliable. The lowest possible injection rate involving no risk of coagulation varies with the blood pressure, the elasticity of the tubing and the damping effect of the needle or catheter. A lower magnitude of pulse pressure permits a lower infusion rate. The greater the elasticity of the tubing the higher the injection rate must be set in order to prevent the blood from flowing into the tubing during systole and gradually clotting. In a narrow and long catheter the pulse pressure is damped fairly effectively, so that the infusion rate can be kept low, while when using a relatively short and wide puncture needle the infusion rate must be kept higher. Under the last-mentioned unfavourable conditions it has proved wise not to use an injection rate less than that corresponding to the third gear; at this rate a 50 ml syringe will last for 15 minutes.

The apparatus has recently been used for the injection of contrast medium in lymphography. The low and constant rate of injection which is easily maintained with the apparatus gives a better filling of the deeper lymph vessels than the uneven, often forced, manual injection. The latter is also liable to injure the vessels.

It may be mentioned that the apparatus has been successfully used for the intra-arterial injection of contrast medium in laboratory animals (Jeppson & Oli 1960).

SUMMARY

An infusion apparatus for the automatic injection of physiologic saline to prevent coagulation in the needle or catheter during angiography is described. The apparatus has also been used for the injection of contrast medium in lymphography as well as in angiography in laboratory animals.

ZUSAMMENFASSUNG

Ein Infusionsgerät für automatische Injektion von physiologischer Kochsalzlösung, um bei Angiographie eine Koagulation in der Nadel oder im Katheter zu verhindern, wird beschrieben. Das Gerät war auch für Injektionen von Kontrastmittel bei Lymphographie wie auch bei Angiographie von Laboratoriumstieren verwendet worden.

RÉSUMÉ

Les auteurs décrivent un appareil de perfusion pour l'injection automatique de sérum salé physiologique, destinée à empêcher la coagulation dans l'aiguille ou le cathéter au cours de l'angiographie. Cet appareil a aussi été utilisé pour l'injection de moyen de contraste en lymphographie et en angiographie sur les animaux de laboratoire.

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VERTEBRAL CATHETERIZATION VIA THE FEMORAL ARTERY

by

STE: CRONQVIST

The direct percutaneous and the catheter methods, of all those proposed for vertebral angiography, are the only two commonly employed. We have in Lund mainly used the catheter technique introduced by RADNER in 1947 but during the last two years a technique with catheterization of the vertebral artery from the femoral artery has been tried as the primary approach in almost all cases. This paper represents an analysis of our experience with this method.

The technique described by RADNER involved exposure of the radial artery, a small ureteric catheter being inserted through an incision in this vessel and manipulated upwards into the vertebral artery.

In 1951 BIERMAN pointed out the possibility of introducing a catheter in the vertebral artery via the femoral artery. LINDGREN (1956) was the first to use this route and to report clinical experiences with the method. His technique consisted of percutaneous puncture of the femoral artery, a catheter being introduced and inserted into the aorta and up to the aortic arch through the needle. The catheter then usually slipped into the left subclavian artery and the contrast medium was injected with the tip of the catheter in the most proximal part of the vessel. If the tip of the catheter could not be passed into the subclavian artery it was left in the part of the aortic arch from which the subclavian artery arises; a larger amount of contrast medium than that used when

Submitted for publication 30 August 1960.

the catheterization of the subclavian artery had been successful was injected in such cases. As both contrast material and a catheter in a vessel may cause spastic contractions LINDGREN avoided placing the tip of the catheter in the vertebral artery.

With the newer contrast media (Hypaque, Urografin 45 %), however, we have found the degree of spasm negligible even in catheterization of comparatively small vessels such as the renal or vertebral arteries. In catheterization via the femoral artery we therefore do not leave the extremity of the catheter in the subclavian artery but insert it into the proximal part of the left vertebral artery. This vessel usually arises from the left subclavian artery, the two arteries together forming an almost straight line with the descending aorta; for this reason a catheter in the aorta can generally be passed directly into the vertebral artery. This, at least, is the rule in young subjects but arteriosclerotic changes with deformation of the aortic arch in the elderly may make the further passage of a catheter more difficult. In the latter instance a slight bend of the catheter about 2 to 3 cm from its tip often helps in the positioning.

If previously we were not successful in placing the catheter in the vertebral artery we would inject a larger volume of contrast medium in either the subclavian artery or in the aortic arch. We now seldom employ such a technique for vertebral angiography since the resulting roentgenograms have been found unsatisfactory.

At the present time, whether catheterizing the femoral or the radial artery, we introduce the catheter in accordance with SELDINGER's technique. A metal wire with a flexible tip is introduced through a needle in the artery which is then withdrawn to leave the wire in the vessel; a polythene catheter is passed over the metal wire and these together are manipulated into the selected vessel.

When the catheter is to be introduced via the radial artery its entry into the vertebral artery is facilitated if a sharp bend of the catheter is made about one centimeter from the tip.

In catheterization via the femoral artery the instruments necessary for the examination consist of a Seldinger needle No 205, a polythene catheter (PA 200) and a corresponding wire leader; with the radial route the number of the needle is 160 and the catheter a PA 160. A radiopaque catheter (ÖDMAN) with a small bore may also be used. General anaesthesia is used only in children. Vasodilating agents have as a rule not been administered. The amount of contrast medium employed is 4 to 5 ml for each injection. Serial films are taken in lateral and in frontal projections.

We have, as stated, regularly tried this type of catheterization in almost all of our cases during the last two years. Among 89 cases, we were successful in placing the catheter in the vertebral artery in 70 (78 %). It may be seen from the Table given below that the majority of failures occurred in those patients who were more than 40 years of age; we failed in 15 out of 38 examinations in which the patients were more than 40 but there were only 4 failures among

Table

Age of patients	Number of patients examined	Catheterization Successful	Catheterization Not successful	Contrast material present in: Posterior choroidal arteries	Post. communic. artery	Carotid siphon	Vertebral artery both sides
< 10	9	9	—	9	8	4	—
10–19	15	14	1	14	11	7	2
20–29	14	13	1	12	10	2	4
30–39	13	11	2	11	5	2	2
40–49	18	12	6	12	6	2	4
50–59	16	10	6	9	3	2	—
60–69	4	1	3	1	—	—	—
> 69	—	—	—	—	—	—	—
Total	89	70	19	68	43	19	12

51 patients studied in the below-40 age group. Thus in this younger group successful catheterization was attained in 92 %. In 2 of the cases recorded as failures, the vertebral artery arose directly from the aortic arch; this anomaly is stated by RADNER to occur in 6 % of cases. No contrast medium to ascertain the origin of the vertebral artery was deposited in the aortic arch in the other two cases nor in the 15 failures encountered in patients over the age of 40.

The vertebral angiographies successfully performed with catheterization via the femoral route were reviewed in order to evaluate the frequency of arterial spasm and to note the degree of intracranial filling of the small arterial branches.

The medial and lateral choroidal arteries were chosen as criteria of a satisfactory angiogram since they are constant, small, have few anomalies, and are of great diagnostic importance. Angiograms were classified as 'good' only when there was filling of these vessels. One case was excluded from consideration because a large arterio-venous aneurysm concealed these vessels.

In one case, spasm of the distal portion of the vertebral artery did not permit filling of its intracranial branches. A slight degree of spasm was also noted in a few other cases but a filling was nevertheless obtained even of the choroidal arteries. Summing up, we noted filling of the posterior choroidal arteries in 68 of 69 angiographies in which catheterization of the vertebral artery had been successful. This means that 98 % of these angiograms were considered as 'good'. In 43 of the 69 angiograms at least one communicating artery was filled (64 %) and in 19 cases (27 %) contrast medium could be seen in the carotid siphon.

For comparison a large number of angiograms performed with direct percutaneous puncture was evaluated using the criteria previously mentioned. All cases with arterio-venous aneurysm were excluded. Of 176 cases the choroidal arteries were filled in 134; only 76 % of the angiograms accordingly were con-

sidered as 'good'. Most of the examinations were made, however, before the apparatus for rapid serial angiography was in use.

Rapid serial angiography was employed in all the examinations performed with catheterization via the femoral artery. In a review of the angiographic filling of the posterior communicating and posterior cerebral arteries, SALTZMAN noticed no significant difference in the degree of filling of these vessels when 'conventional' studies were compared with rapid serial angiograms. Thus the results obtained with the two different types of examination — catheterization on the one hand and direct percutaneous puncture on the other — may reasonably be compared.

Various investigators have published their experiences with the percutaneous puncture technique. LINDGREN (1950) reported filling of the arteries in the posterior fossa in two-thirds of cases in or above middle age. SJÖGREN in a material of more than 150 cases succeeded in puncturing the vertebral artery in all but 2 cases; in 10 cases the filling of the intracranial branches of the vertebral artery was not satisfactory. The major problem in percutaneous puncture, as pointed out by SJÖGREN, is to maintain the tip of the needle in the correct position within the vessel. Various needles have been designed to facilitate this (SJÖGREN 1953, SHELDON 1956, SWANN 1958). SWANN (1958) reported successful examinations in 94 % of the cases in which a modified Sheldon needle was employed; SWANN's earlier experiences with conventional needles were not satisfactory, success being attained in only 60 % of cases examined. RUGGIERO et coll. (1958) succeeded with percutaneous puncture in 225 out of 227 examinations (99.1 %); 33 of the examinations were not satisfactory enough to permit a definite diagnosis. This means that in 194 cases or 85.5 % the authors considered the resulting angiograms acceptable.

RADNER and HAUGE reported successful catheterization with the Radner technique in 98 and 98.5 % of cases, respectively. In 1953, OLSSON added another 140 cases to those already published by RADNER. In this series right-sided catheterization failed in 3 cases but the examination was completed by catheterizing the left side; in one case the examination was interrupted by arterial spasm. BONTE, RIFF & SPY (1958) described the results in 75 angiographies in patients ranging from 6 to 70 years of age. These investigators used the catheter technique as described by LINDGREN. In their series it was possible to place the tip of the catheter in the left vertebral artery in 23 cases and in the right vertebral artery in one case; in 19 cases it lay in the first part of the subclavian artery and in 2 cases in the aortic arch at the origin of the left subclavian artery. These authors considered the examination to have been successful in 45 cases or 60 %.

The two catheter methods, as well as the puncture technique, have advantages as well as disadvantages. Percutaneous puncture of the vertebral artery may be a painful experience to the patient, while a puncture of the radial or femoral artery is readily tolerated. Some of the arguments raised against the

Radner technique also apply to catheterization via the femoral artery. Thus, sterile conditions and fluoroscopy are required. The Seldinger instruments, however, will minimize the trouble caused by the necessity for a sterile field and the fluoroscopic exposure will be kept within reasonable limits by attention to the size of the diaphragm and by keeping the viewing time down to under a minute. The use of an image amplifier will decrease the amount of radiation delivered both to the operator and to the patient as will the use of the TV technique. This has lately been employed at Lund. The latter will also minimize the risk of soiling the sterile instruments which otherwise may easily happen when working with fluoroscopy in the dark.

All methods for the examination of the vertebral artery have a common disadvantage, that is, the inconstant filling of the posterior inferior cerebellar artery on the opposite side. When the involved side is indicated by the clinical findings, this side may readily be selected if the percutaneous puncture method is employed. Routine use of the Radner technique or the Lindgren technique implies that the right or the left vertebral artery, respectively, is examined. It is possible to catheterize the left vertebral artery from the left arm and conversely the right vertebral artery from the femoral route. This involves, however, a more extensive and difficult manipulation. In order to overcome this disadvantage one may attempt to fill the opposite posterior inferior cerebellar artery by injection during diastole (Olin 1958), or by compression of the opposite vertebral artery as described by Saltzman. The last-mentioned method, however, as well as any other manipulations of the head may be employed to best advantage in the catheter method. The use of the percutaneous route on the other hand will increase the difficulties in maintaining a correct needle position during such manipulations.

Complications following vertebral angiography have not been confined to one particular technique. Nevertheless a review of the literature would seem to indicate that the catheter method, as originally applied by Radner, is followed by more complications than the direct percutaneous puncture (Radner 1951, Olsson 1953, Hauge 1954, Sjögren 1953, Swann 1958, Ruggiero 1958, inter alios).

In the author's cases with catheterization of the vertebral artery via the femoral artery there was only one alarming cerebral complication associated with vertigo, nystagmus, vomiting and a fall in blood pressure. The signs were transitory, however, and completely disappeared in half an hour.

SUMMARY

The technique of catheterization of the vertebral artery is described. Catheterization via the femoral route was found to be more successful in patients below than in patients above the age of 40. The resulting angiograms were of good quality and filling of smaller arterial branches was seen more often than in angiograms performed with direct percutaneous puncture of the vertebral artery.

ZUSAMMENFASSUNG

Die Technik der Katheterisierung der A. vertebralis wird beschrieben. Die Katheterisierung auf dem femoralen Wege war bei Patienten im Alter von unter 40 Jahren erfolgreicher als bei denen, die älter waren. Die so erzielten Angiogramme waren von guter Qualität und die Füllung kleiner Arterienäste wurde hier öfter als in den Angiogrammen beobachtet, die nach direkter perkutaner Punktion der A. vertebralis hergestellt wurden.

RÉSUMÉ

L'auteur décrit la technique du cathétérisme de l'artère vertébrale. Le cathétérisme par voie fémorale est plus souvent couronné de succès avant qu'après l'âge de 40 ans. Il donne des angiographies de bonne qualité et opacifie plus souvent les fins rameaux artériels que les angiographies exécutées par ponction percutanée directe de l'artère vertébrale.

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LOCALIZATION WITH Sr^{85} OF SPINAL METASTASES IN MAMMARY CANCER AND CHANGES IN UPTAKE AFTER HORMONE AND ROENTGEN THERAPY

A preliminary report

by

INGE GYNNING, PER LANGELAND, STURE LINDBERG and BERNDT WALDESKOG

Skeletal metastases are often not demonstrable in the roentgenogram until bone destruction is considerable. This applies particularly to the spine. A comparison between roentgen and postmortem findings, as well as experimental studies by BABAÏANTZ, have shown that the bone decalcification must reach about 50 % before it is evident in the roentgen film.

Investigations with so-called osseophil isotopes in recent decades have contributed considerably to our knowledge of the mineral metabolism of the skeleton. Such isotopes have also been used in the elaboration of methods enabling an earlier diagnosis of osseous tumours. The distribution of radiogallium (Ga^{66}, Ga^{67} and Ga^{72}) in the skeleton and their concentration in osseous lesions, particularly tumours, have been studied by DUDLEY et coll. (1950, 1956), DESGREZ (1954), DESGREZ et coll. (1954) and MULRY et coll. They have shown that occasionally an accumulation of radiogallium may be demonstrated in osseous tumours before it can be detected at roentgen examination.

The method has been used in examinations for primary osseous tumours as well as skeletal metastases. DESGREZ et coll. claim to have shown that a tumour is sometimes more extensive than may be assumed from its roentgenographic appearance, an observation of importance in the radiotherapy

Submitted for publication 25 August 1960.

of the lesion. According to DESGREZ et coll. and DUDLEY et coll. (1956) irradiation can depress the readiness with which a tumour takes up radiogallium.

Recent investigations have revealed that strontium has a more specific affinity for bone than gallium and must therefore be preferred in examinations for osseous tumours. The first to use radiostrontium clinically were TREADWELL et coll., who as early as 1942 showed that Sr^{89} accumulates in neoplastic osseous tissue. Their observation has since been confirmed by BAUER for example, who used Sr^{85}. BAUER et coll. (1957, 1958, 1959, and work not yet published) have studied osseous metabolism not only by urine analysis and measurement of the radioactivity of the blood but also by external measurements for which they used mainly Sr^{85} and Ca^{47}. They studied tumours as well as a number of other osseous conditions and gave information of clinical value regarding the diseases in which an increased uptake may be expected.

The investigations referred to above prompted us to study the uptake of Sr^{85} by the spine in patients operated upon for cancer of the breast. The purpose of the investigation was to assess the value of the isotope for making an early diagnosis of spinal metastases, for charting the spread of the tumour, and for comparing the uptake of the isotope by the lesions before and after different types of treatment (local roentgen irradiation and hormone treatment). In order to permit a comparison between the value of the isotope technique and the roentgen examination in the early diagnosis of osseous tumours of the spine, roentgenograms were taken every time the isotope was injected.

Sr^{85} is a pure gamma ray emitter with an energy of 0.51 MeV; its half-life is 65 days. For each examination the patient received 50 μC Sr^{85} intravenously.

Measurements were made with an EKCO scintillation detector mounted in an LKB collimator. The latter can be provided with different cones, and in the present investigation a cone with a 12° opening angle and a diameter of 65 mm was used. Pulses from the photomultiplier were amplified in an EKCO linear amplifier and then fed into a Tracerlab superscaler via a single-channel pulse analyzer. The 'window' used was placed over the gamma peak. The apparatus was the same as that used by BAUER et coll. (1959). The stability of the apparatus was continuously checked. For this purpose Na^{22} was used as well as a stock solution of Sr^{85}. All of the measurements were normalized against the counting rate of the stock solution. This was determined before and after measurement on the patient, and a mean value was used for the normalization.

Measuring technique. Measurements were made at 10 levels of the spine, spaced 6 cm apart. This distance was selected because the collimator cone with an opening of 65 mm diameter covered about 10 cm of the spine. Measurements were also made as a routine bilaterally over a point situated centrally at the upper border of the patella. This was done to obtain values for a part of the skeleton which was probably not involved by metastases and in which

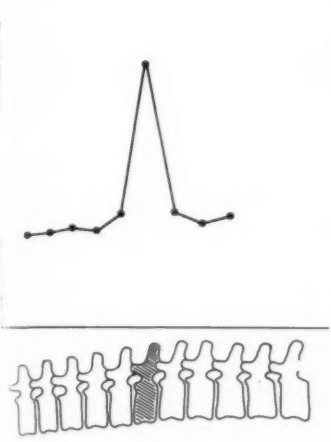

Fig. 1

Fig. 1. Curve illustrating a high counting rate over a vertebra with metastases 7 days after injection.

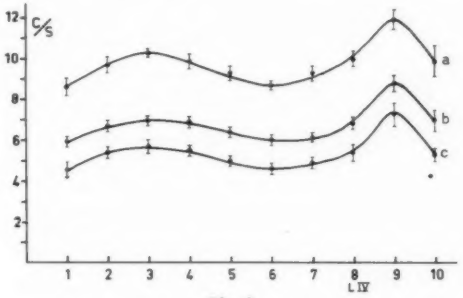

Fig. 2

Fig. 2. 'Normal' curve for activity over spine. Counting rates determined over 10 levels of the spine: a) 1 week, b) 2 weeks, and c) 3 weeks after injection of 50 μC Sr^{85}.

metastases, if present, could be readily detected by variation in the quotient between the values obtained over the two knees. These measuring points are easy to identify. The outer aperture of the collimator was placed directly against the skin and the time for 1 000 counts was noted. Two determinations were made over each measuring point with reposition of the detector. Each patient was studied one, two, and three weeks after the injection. When the roentgen examination suggested pelvic metastases, measurements were made over the suspected area as well as over the corresponding contralateral area.

A repeat series of measurements were performed, usually at an interval of about 6 months. The activity over the spine and the knees was also measured before the injection of the isotope for such repeat studies. These basic values were subtracted from the measuring values found after the repeated injection. The detector was placed over the same measuring points as on the previous occasion with the aid of roentgenograms with markers.

For judging to what extent an accumulation of Sr^{85} in metastases might be expected, a number of patients with known skeletal metastases were studied. All the patients showed a marked accumulation of the isotope in the region with roentgen changes (Fig. 1).

Examinations were later made of a number of patients with tumour but without probable skeletal metastases. This preliminary examination of 7 selected patients with a roentgenologically normal spine, apart from insignificant osteitis deformans changes, showed the differences in the counting rate over corresponding points to be surprisingly small. Mean values of the counting rate over the 10 measuring points in these 7 cases were therefore calculated

Table

Group	A $0.9 \leq f < 1.5$	B $1.5 \leq f < 2.0$	C $f \geq 2.0$	Number of cases	Metastases, fractures shown by roentgen
I Normal shape of spine activity curve.....	27	9	2	38	0
II Abnormal shape of spine activity curve.....	0	8	24	32	18

and plotted as a function of the measuring points (Fig. 2). The curves are based on measurements made one, two and three weeks after the injection of strontium. The curves showed one peak over the middle thoracic spine and another over the sacro-lumbar region. The shape of the curve is due mainly to the volume of the skeleton covered by the detector and to variations in the distance between the skeleton and the detector owing to the curvature of the spine. The curve obtained for the spine is hereinafter referred to as the 'normal curve'. No appreciable difference was found in any of these seven cases between the values noted over the two knees.

A question often requiring consideration in the planning of treatment of a large group of patients with cancer of the breast is whether there is any suggestion of skeletal metastases. A total material of 70 cases of cancer of the breast were therefore selected for clinical trial, almost half of them (30 cases) immediately after the operation. The latter belonged to stage II group 3 according to NOHRMAN's nomenclature and had thus had metastases in the axillary lymph nodes with a periglandular spread. It is known that 75 % of such patients must be expected to die within 5 years; within this period this group will therefore probably include a relatively large number of cases with skeletal metastases. Examination with Sr^{85} was repeated at intervals of about 6 months. The purpose of this long-term investigation was to ascertain whether by this method skeletal metastases could be detected earlier than in the roentgen examination. In some cases this appeared to be possible.

The rest of the series (40 cases) consisted of cases of cancer of the breast with roentgenologically demonstrated or clinically suspected skeletal metastases.

After the curves had been compared with the normal curve the material was first divided into two groups according to the measurements made over the spine. Cases with a spine curve of normal configuration, irrespective of the level of the curves, were assigned to the first group and those with an abnormal configuration to the second group.

Of the whole material of 70 cases, 38 belonged to group I and 32 to group II, as may be seen from the Table above. A detailed analysis of these cases is in progress.

These two groups were divided into three subgroups A, B and C, according

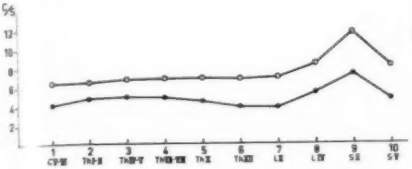

Fig. 3. Measurements at 6-month intervals. The second curve is higher but of same shape as the first one. ● August 21st, 1958; ○ February 4th, 1959.

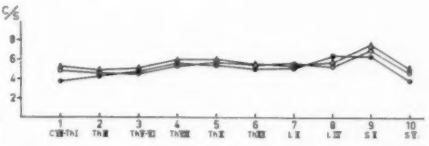

Fig. 4. Measurements at 6-month intervals with no manifest changes in the general condition or in the roentgen findings. Good agreement between the curves. ● September 18th, 1958; ○ March 10th, 1959; △ September 10th, 1959.

to the highest value for the factor *f*, which is the quotient between the measured value and the corresponding normal value.

It is clear from the table that in the majority of the cases in group I the highest factor was below 1.5, while none of the cases in group II lay in this subgroup. In sharp contrast, a factor of more than 2 was found in only 2 cases in group I against 24 in group II.

No spinal metastases or fractures were roentgenologically demonstrable in group I. One of the patients belonging to group II: B had metastases, while 14 patients in group II: C had spinal metastases and 3 had compression fractures. No explanation can be offered for the abnormal measuring values or the configuration of the spine curve in those cases in which roentgen examination had shown no signs of a pathologic condition. Repeated Sr^{85} tests and roentgen examination at relatively short intervals as well as autopsy findings may with time provide an explanation for the variation in the order of magnitude of the factor *f* and of the configuration of the curve. All that can be said for the time being is that any appreciable deviation from the normal configuration of the curve suggests metastases.

The long-term investigation of cancer of the breast stage II:3, which is in progress, with regular examination of the distribution of Sr^{85} at 6-monthly intervals and comparison with the roentgen findings, has already yielded useful information. It has been found, for example, that advanced osteitis deformans may give high values and, as demonstrated previously by BAUER et

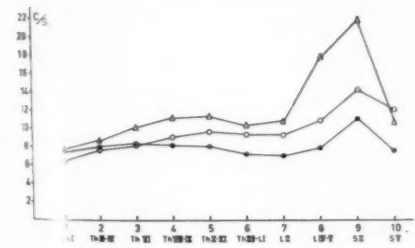

Fig. 5. Case of mammary carcinoma stage II group 3. Primary normal spine activity curve. Increasing values with maximum in the lower lumbar region indicating metastases. Roentgen examination negative. ● March 18th, 1959; ○ September 16th, 1959; △ March 19th, 1960.

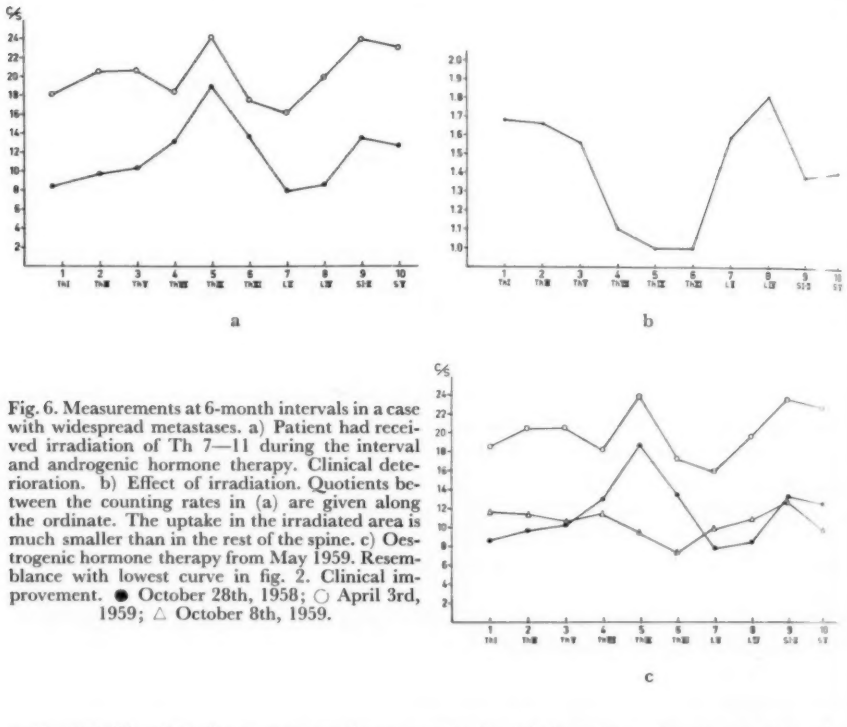

Fig. 6. Measurements at 6-month intervals in a case with widespread metastases. a) Patient had received irradiation of Th 7—11 during the interval and androgenic hormone therapy. Clinical deterioration. b) Effect of irradiation. Quotients between the counting rates in (a) are given along the ordinate. The uptake in the irradiated area is much smaller than in the rest of the spine. c) Oestrogenic hormone therapy from May 1959. Resemblance with lowest curve in fig. 2. Clinical improvement. ● October 28th, 1958; ○ April 3rd, 1959; △ October 8th, 1959.

coll. (1959), that fractures produce markedly high values. In some cases the level of the curve varied slightly in the absence of any manifest change in the general condition of the patient (Fig. 3). As will later be apparent external factors such as endocrine balance may be of significance. In some cases good agreement was found between the values noted on different occasions (Fig. 4).

It was as mentioned considered of interest to ascertain whether it is possible to demonstrate changes earlier by means of Sr^{85} than by roentgen examination. Slight changes in the roentgenogram were often not detected until re-examination after Sr^{85} had in fact suggested the possibility of these being present. In some cases, however, no agreement was found between the two methods (Fig. 5). The shape of the spine curve was normal at the time of the initial measurement, with a highest factor of 1.6. On re-examination half a year later the values found for the lower spine had increased with a maximal factor of 1.8 and at the final measurement, 1 year after operation, the values had increased further, with a considerable change in the shape of the curve 1 and a maximal factor of 3.2 over the fourth lumbar vertebra and of 2.9 over the second sacral vertebra. The patient felt well and roentgen examination showed no signs of

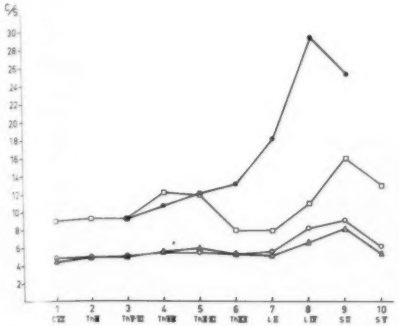

Fig. 7. Measurements in a case with widespread metastases. Irradiation of lumbar spine in February—March 1958. Androgenic hormone therapy. Resemblance with lowest curve in fig. 2. Clinical improvement. Hypercalcaemia in middle of 1959. Androgenic hormone therapy replaced by cortisone. Deterioration. ● March 27th 1958; ○ November 5th, 1958; △ May 13th, 1959; □ December 1st, 1959.

spinal secondaries. Metastases, however, were found in L 4 on further roentgen examination 2 months later. It is thus evident that Sr^{85} can detect skeletal metastases before they give rise to symptoms and it would therefore appear that the method is a useful supplement to the routine roentgen examination.

The isotope technique was also studied for its capacity to reveal the effect of palliative treatment of cases with widespread skeletal metastases. For this purpose patients were selected in whom a series of Sr^{85} measurements had been made on three or four occasions after irradiation or institution of hormone therapy. The first test was performed at the beginning of treatment. The examinations are of particular interest with respect to those changes that can be recorded in the isotope uptake and correlated with the clinical course after therapy has been started.

Case reports

Case 1. A woman, aged 54, operated upon in 1947 for cancer of the breast stage I who when returning 11 years later complained of pain in the lower thoracic spine. Roentgen examination revealed widespread metastases in the ribs, spine and pelvis. In October 1958 Sr^{85} showed increased values over all measuring points of the spine and an irregular curve (Fig. 6a). The patient was given androgenic hormone therapy. A month later she was submitted to bilateral oophorectomy, after which she received roentgen irradiation of the lower thoracic spine and, later of the lumbar spine. In April 1959 a general further increase of the Sr^{85} values was noted; within the area irradiated four months previously the increase was, however, relatively smaller. The patient felt worse with increasing pain, and further roentgen examination showed progression of the metastases. The relatively smaller increase in the counting rate over the irradiated area was noteworthy and was ascribed mainly to the irradiation, in accordance with previous investigations with radiogallium. In an attempt to elucidate this, the quotients between the counting rates over the corresponding points were plotted as a function of the 10 measuring points (Fig. 6b). The quotients were normalized to point 5 (Th 9). The figure clearly shows the difference in the counting rate between the non-irradiated and irradiated areas.

New measurements were made after androgenic hormone therapy had been replaced by

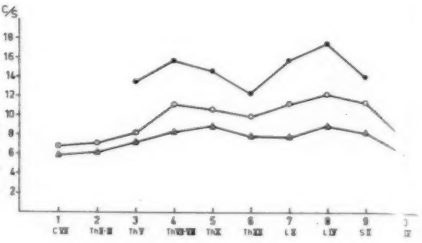

Fig. 8. Measurements in a case with widespread metastases. Androgenic hormone therapy. Resemblance with lowest curve in fig. 2. Clinical improvement. ● March 1st, 1958; ○ August 19th, 1958; △ February 14th, 1959.

oestrogenic hormone therapy a month later. The patient had improved and at the time of this measurement a fall was noted in the values recorded over all points (Fig. 6c).

Case 2. A woman, aged 57, operated upon for cancer of the breast stage I in 1949 who returned 9 years later complaining of skeletal pain. On roentgen examination widespread metastases of the spine and pelvis were found. In February 1958 she had received irradiation of the lumbar spine and was afterwards submitted to bilateral oophorectomy followed by androgenic hormone therapy. The first Sr^{85} test was performed a month later. Measurement showed generally increased values over the entire spine with a maximum over the lumbar region (Fig. 7). Following treatment the patient was free from symptoms and at two subsequent examinations with Sr^{85} the spine curve was found to be almost normal. This was interpreted also as an effect of therapy. Roentgen examination showed an improvement in the calcium content of the affected bones and a recovery of skeletal structure.

Hypercalcaemia secondary to treatment with androgenic hormone occurred just over a year later and the treatment had to be withdrawn. This was followed by pain in the lower thoracic spine. Re-examination with Sr^{85} showed that the values had again begun to rise and were highest over the region of the pain. The patient has since been treated with androgenic hormone combined with cortisone, the pain has disappeared, her general condition has improved and she is able to carry on with her usual work.

Case 3. A woman, aged 49, with inoperable, ulcerative cancer of the breast was treated with roentgen irradiation and afterwards by mastectomy. Roentgen examination showed a left pleural effusion and skeletal metastases. The patient was treated with radioactive gold to the pleura and bilateral oophorectomy followed by androgenic hormone therapy. The pain disappeared and the patient felt better. No roentgen treatment was given. The Sr^{85} curve plotted at the beginning of the hormone therapy was abnormal (Fig. 8). Also in this case the shape and level of the curve on two later occasions tended to return to normal on clinical improvement of the patient.

In those cases in which hormone therapy produced clinical improvement the values and the shape of the Sr^{85} curve tended to return to normal, while clinical deterioration was accompanied by a rise in the Sr^{85} values.

The observations set forth above are based on preliminary examinations. They will be supplemented by detailed analyses of the excretion of strontium in the urine of cases with skeletal metastases and in normal controls. In this long-term study an analysis of the blood, urine, and faeces in special cases will also receive due attention. A scintillographic technique for examining selected parts of the skeleton is being devised.

SUMMARY

An isotope technique with Sr^{85} for detecting metastases in mammary carcinoma by external measurement of the radioactivity over the spine is described with reference to a material of 70 cases. The method is a good complementary method in the routine examination of patients with cancer of the breast and will sometimes demonstrate metastases earlier than roentgen examination. Changes in the isotope uptake in association with palliative irradiation and hormone therapy are exemplified.

ZUSAMMENFASSUNG

Eine Isotoptechnik mit Sr^{85} zur Entdeckung von Metastasen bei Mammakarzinomen mit Hilfe externer Messungen der Radioaktivität über der Wirbelsäule wird unter Bezugnahme auf ein Material von 70 Fällen beschrieben. Die Methode ist ein gutes Komplement bei der üblichen Untersuchung von Patienten mit Brustkrebs und erlaubt es, gelegentlich Metastasen frühzeitiger zu demonstrieren als es mit Hilfe der Röntgenuntersuchung möglich ist. Veränderungen der Isotopenaufnahme bei gleichzeitiger palliativer Bestrahlung und Hormontherapie werden mit Beispielen belegt.

RÉSUMÉ

Les auteurs décrivent, sur un matériel de 70 cas, une technique isotopique avec Sr^{85} pour détecter les métastases du cancer du sein, par la mesure externe de la radioactivité au dessus de la colonne vertébrale. Cette méthode est un bon complément de l'examen standard des malades atteintes de cancer du sein et mettra parfois en évidence des métastases plus précocement que l'examen radiologique. Les auteurs donnent des exemples de modification de la fixation de l'isotope sous l'effet de la radiothérapie palliative et de l'hormonothérapie.

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CLEANSING OF THE LARGE BOWEL BEFORE ROENTGENOLOGIC EXAMINATION OF THE ABDOMEN

by

ROLF KÖHLER and ESKO TÄHTI

An essential condition for the achievement of a good result in the roentgen examination of the abdomen is a satisfactory preparation of the large bowel. The object of the present work was to find out which of three methods of evacuation cleanses the colon most effectively, to discover which method is the least time-consuming for the nursing staff and the patient seems to prefer, to find out whether the patient's age has any effect on the efficacy of the preparation, and to establish whether and to what extent prolongation of the interval between the last cleansing measure and the roentgen examination affects the distribution of gas in the stomach, small intestine and colon.

Methods and Material

The cleansing methods were as follows.

A. The day before the examination the patient was kept on a light diet and at 10 a. m. given 15 ml castor oil per os, and in the evening in the ward an enema of 1.5 l water, the latter being repeated on the morning of the examination.

B. A light diet the day before the examination and at 10 a. m. 15 ml castor oil per os. On the morning of the examination an enema of 1.5 l water was

Submitted for publication 29 June 1960.

given with one container of Clysodrast Novum (Ferrosan, Malmö, Sweden), a preparation consisting of 4.4-diacetoxidiphenyl-pyridil-(2)-methane and tannin.

C. A light diet the day before the examination and at 7 p. m. 3 tablets of Metalax 0.005 g (Star, Tampere, Finland, to whom we are indebted for the tablets as well as the suppositories). The evacuating component is identical with that in Clysodrast and is contact laxative which affects only the large bowel. On the morning of the examination the patient received 1 Metalax suppository 0.01 g an hour before the beginning of the examination. In investigations of the colon the evacuation was commenced the day before at 3 p. m. with 1 Metalax suppository. For the pharmacologic and physiologic effects of the substance reference is made to EKLÖF (1958) who used Dulcolax (C. H. Boehringer & Sohn, Ingelheim am Rhein, Western Germany) of the same composition as Metalax.

The cleansing results in 567 patients were compared; 240 were to undergo urography, 191 cholecystography and 136 an examination of the colon. The material also included as controls 100 outpatients who had not been prepared. 115 ward patients were prepared by the method A with a cleansing enema, and 105 by method B with Clysodrast; 138 outpatients and 209 ward patients were prepared by method C with Metalax.

An ordinary film of the abdomen was obtained half an hour to three quarters of an hour after the last evacuation. The volume of gas in the stomach, small intestine and colon and the volume of the colonic contents were classified as follows: (I) excellent = insignificant amounts of gas in the alimentary tract, (II) good = only small amounts of gas in the alimentary tract or a very scanty colonic content, (III) fair = moderate amounts of gas or colonic contents, enough to interfere with the diagnostic evaluation of the films, (IV) poor = much gas or large residues in the alimentary tract, making it impossible to perform a satisfactory evaluation.

A further routine film was taken in 174 cases one hour after the first to determine how the longer interval between the evacuation and examination affected the volume of gas in the organs concerned.

Results

Colonic evacuation. The distribution of the results in the control material and after evacuation according to methods A, B, and C are shown in the Diagram, p. 131. The cases treated according to method C have been divided into an outpatient and a ward patient group. As may be seen from the diagram, the evacuation following Metalax was the most complete, with little difference between outpatients and inpatients; in nearly one-third of the cases, castor oil and an enema gave a poor result, and the same was true of

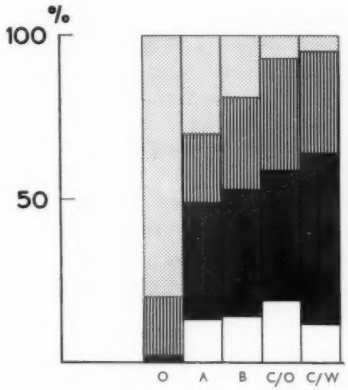

Diagram showing the results of assessment of the volume of gas and the colonic contents in control patients and patients evacuated with the aid of methods A, B, and C. The percentual distribution into four groups is according to the classification given in the text. O = control patients, C/O = method C on outpatients, C/W = method C on ward patients. White sections indicate excellent, black sections good, striped sections fair, and dotted sections poor evacuation.

castor oil and Clysodrast in just under one-fifth of the cases. It is worthy of note that 2 % of the unprepared patients ranged into group II and 16 % into group III.

As already mentioned, the enema was given in the wards. This is probably the principal reason why the result in the group treated according to method A was unexpectedly poor. An enema is effective only if administered by specially trained personnel and can be done best in the roentgen department. This view was expressed by WELIN (1958) whose results with Clysodrast Novum enemas given in the roentgen department were excellent and constituted a firm foundation for the successful application of the double contrast method in examinations of the large bowel.

Technical nursing aspects of colonic evacuation. Cleansing of the bowel by means of tablets and suppositories requires only a minimal expenditure of time by the nursing staff, and in this respect is far superior to the enema. Of the irrigation methods, Clysodrast is the slowest, as the patient often experiences abdominal pain, though this passes over if there is a short pause in the filling of the bowel. Metalax has been greeted with satisfaction by the staff in the heavily over-worked and cramped conditions of the outpatient department. The large accumulation of morning enemas has been reduced by the home-preparation for the roentgen examination. Of the 120 ambulant cases questioned, 78 % professed to prefer Metalax purgation to an enema, principally because the former causes less discomfort.

The laxative effect of Metalax tablets usually began in 8 to 12 hours, the stools being mostly of a loose consistency. The tablets proved ineffective in 8 % of the cases; when this happened, the bowel was emptied with the aid of a Metalax suppository which failed to produce an effect in only 5 cases. In two-thirds of the cases the suppository had a latent period of 15 min and

the range of the latency was 1 to 75 min. This concurs with the experience of other workers (ZIMMERMANN 1957, MIES 1957, EKLÖF 1958). There were occasional cases in which the patient complained of abdominal pain at night and of somewhat disturbed sleep. Nausea occurred in 5 % of cases.

Effect of the patient's age on the evacuation result. The influence of the patient's age on the result of the evacuation was investigated. 213 patients belonged to the age group 20—40 years, 257 to the 40—60 years age group and 97 patients were over 60 years of age. The percentage distribution was about equal in all three groups. It appears that the patient's age has no obvious influence on the evacuation result.

Effect of the time lapse after evacuation on the volume of gas in the colon. A further routine film was taken in 175 cases one hour after the first in order to find out whether and to what degree the distribution of gas in the alimentary canal was affected by this delay. In these 175 cases, as well as in all the other cases of this material, the patients were ambulatory. The patients were examined erect; an examination performed with the patient recumbent would very probably have produced a different distribution of gas, but this has not been more closely investigated in connection with the present work.

There was an equal incidence of increase and decrease in the amount of gas in the stomach in a third of the cases. If the gas in the stomach diminished, the amount of gas in the small intestine or the colon, sometimes in both, always increased. The volume of gas in the small intestine changed during the interval in 23 % of the cases and with few exceptions it increased. The amount of gas increased in the colon in 34 % of the cases and it never diminished. The changes in volume were about the same in all groups in all parts of the alimentary tract.

Conclusions

The preparation of the colon with castor oil and a water enema, castor oil and a Clysodrast Novum enema, and a tablet and suppository contact laxative of the dioxyphenylisatin type (the substance which is also contained in Clysodrast) was compared in a material of 567 patients.

Tablets and suppositories gave the best results and were the most convenient. The enemas were given in the wards, probably the principal reason for the results being rather poor. With a trained staff, however, it is also possible to achieve good evacuation results with a Clysodrast Novum enema and this agent is used in the author's department prior to any double contrast medium studies of the large bowel.

The age of the patient had no effect on the evacuation result. The roentgen examination should be started as soon as possible after the colonic evacuation; a delay of one hour increased the volume of gas in every third patient.

SUMMARY

A comparative study was made in 567 cases of the results of preparation of the colon by castor oil and a water enema, castor oil and Clysodrast Novum enema, and tablets and suppositories containing the same contact laxative as Clysodrast, viz. dioxyphenylisatin. The most effective evacuation of the colon was produced by the last method.

ZUSAMMENFASSUNG

In 567 Fällen wurde eine vergleichende Studie über die Resultate der Vorbereitung des Dickdarmes mit folgenden Medikationen unternommen: purgativem Öl und Wassereinlauf, Öl und Clysodrast-Novum Einlauf, und Tabletten und Suppositorien, die dasselbe Kontaktlaxans wie Clysodrast, i. e. Dioxyphenylisatin, enthalten. Die wirksamste Entleerung des Dickdarmes wurde mit der letztgenannten Methode erzielt.

RÉSUMÉ

Les auteurs ont comparé sur 567 cas les résultats de la préparation du colon par l'huile de ricin et un lavement d'eau, l'huile de ricin et un lavement au Clysodrast Novum, et des comprimés et des suppositoires contenant le même laxatif de contact que le Clysodrast, c'est-à-dire la dioxyphénylisatine. C'est cette dernière méthode qui donnait la meilleure évacuation du colon.

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CONTRAST MEDIUM ACCUMULATION IN PARA-AORTIC LYMPH NODES DURING LUMBAR AORTOGRAPHY

Report of a case

by

HERMAN LODIN

Lumbar aortography is of considerable importance in the differential diagnosis of the causes of hypertonia, both with regard to the demonstration of tumours (phaeochromocytomata) producing this condition and in the identification of changes in the renal tissues and vessels.

The following case has features of interest concerning the differential diagnosis of para-aortic tumours in which abnormal vessels are demonstrable.

A boy, aged 9 years, had, when 6 months and again when 18 months old, had acute pyelitis. Following the attacks the Heller test for albumin had for many years occasionally been positive; the blood pressure recorded when he was 6 years old was 160/110. When admitted for investigation the blood pressure was 190/175 to 145/120. The non-protein nitrogen was 33 mg %, Heller's test was positive, and Esbach's reaction 0.4 ‰. The urinary sediment contained numerous red and white blood cells. Renal concentration tests gave a figure of 1.01; the endogenous creatinine clearance was 101 ml, the insulin clearance 113 ml, the PAH clearance 406 ml, and the urinary catechol level was normal.

Urography. The right kidney was enlarged, the left small. Good function on the two sides. The upper calyces of the kidneys were slightly dilated, but not otherwise abnormal. A double renal pelvis and ureter were present on the left side, and the left renal cortex was markedly reduced (only about 2 mm in thickness).

Submitted for publication 31 August 1960.

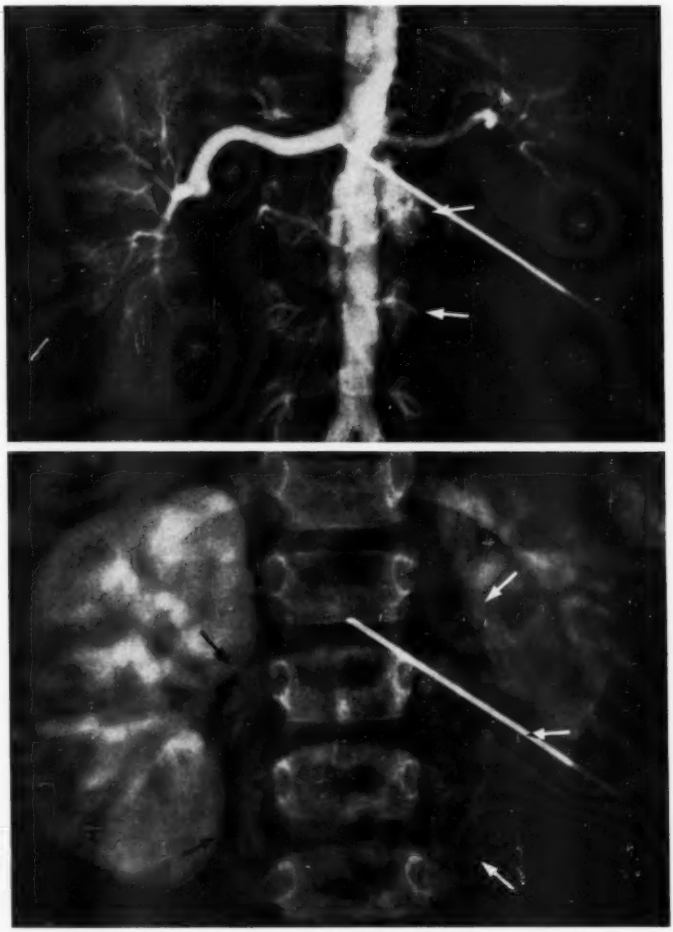

Fig. 1. Lumbar aortography. Large right kidney with slightly irregular upper pole. Normal arterial and nephrographic phases. Small left kidney with thin cortex and reduced vascular supply. Two tumour-like structures lie immediately below the narrow left renal artery (top view). Numerous tortuous vessels are evident to the right and left of L2 and L3 and within a clearly defined zone in front of these vertebrae (lower view).

Lumbar aortography (Fig. 1). Two tumour-like structures, the size of a walnut and of a pea respectively, were evident close to the aorta, immediately below the left renal artery. Fairly wide tortuous vessels and a collection of contrast medium were evident in these regions and to a less extent in front of L2 and L3 and to the right of the aorta at the same level. The

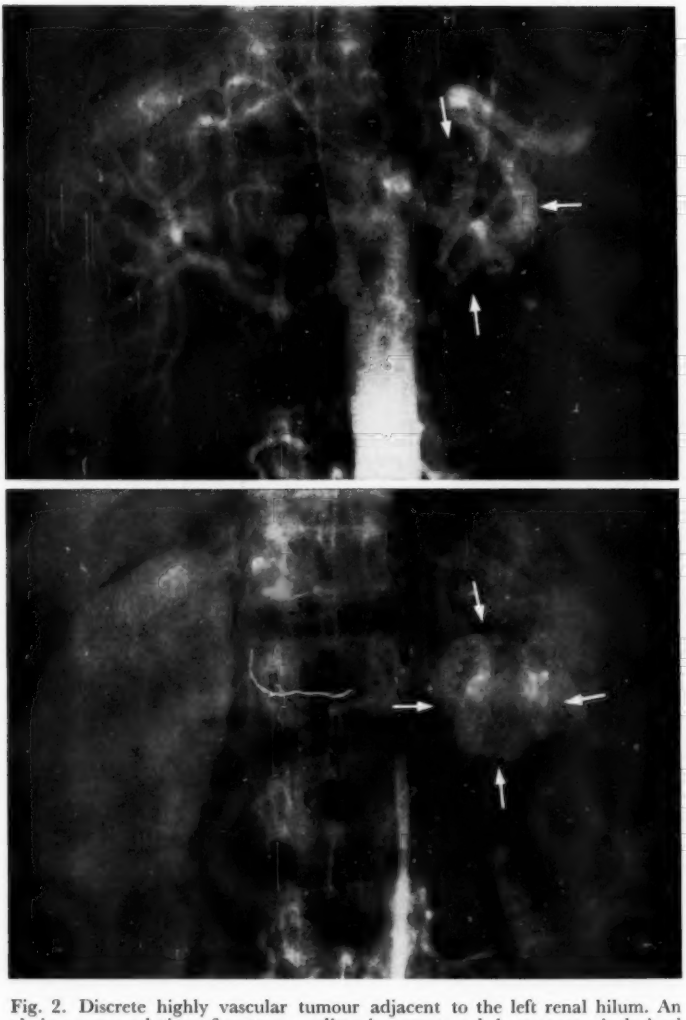

Fig. 2. Discrete highly vascular tumour adjacent to the left renal hilum. An obvious accumulation of contrast medium is present and the structure is drained by a large vein (phaeochromocytoma).

right renal artery was wider than the left. The right kidney was enlarged, with the upper pole slightly irregular in shape. The intrarenal vessels and the nephrographic effect were normal. The left kidney was small and rather irregular in shape with few vessels; the cortex in places was very thin. The nephrographic effect was normal. The adrenals showed a normal

va ular pattern and were of the usual size. The investigation thus disclosed highly vascular pa -aortic tumours and fibrosis of the left kidney.

peration. A series of tumours with the macroscopic appearances of lymph nodes were evi ent along the aorta, corresponding in position to those demonstrated on aortography. Th left kidney presented the changes seen after repeated attacks of pyelonephritis and was re ved. Microscopic examination proved the para-aortic 'tumours' to consist of lymph no les with slight, unspecific changes; the left kidney showed evidence of pyelonephritis.

llowing operation the blood pressure fell to 125/120—95/80, indicating that the left kid y had been responsible for the hypertonia.

Discussion

umours giving rise to hypertonia may be found at sites other than the adrenals and then commonly adjacent to the aorta (cf. Fig. 2). Abnormal vessels and an abnormal accumulation of contrast medium may occur in these tumours. EDSMAN (1957) reported pathologic vessels in one case and an accumulation of contrast medium in another in 3 cases of phaeochromocytomata. ELFVIN (1959) collected from the literature 8 phaeochromocytomata (including EDSMAN's) and discussed them together with a new case of his own; of these 9 tumours 7 had pathologic vessels. Abnormal vessels may also be found in other tumours of the adrenal region, namely malignant adenomata, malignant neurinomata and neuroblastomata.

Our case had pyelonephritic contracture of the left kidney, which alone would account for the hypertonia; the urinary catechol level was normal. The finding of para-aortic tumour-like structures on aortography was a further indication for operation; the fact that the structures were bilateral suggested that they were not connected with the pathologic left kidney.

The tumour-like structures were identified as lymph nodes and showed slight unspecific inflammatory changes; there was no evidence of malignancy. The roentgenographic demonstration of vessels in lymph nodes must be very rare and, as far as I am aware, has not previously been reported. LINDGREN, however, has in two cases observed pathologic vessels in lymph nodes invaded by tumour tissue from a hypernephroma.

The presence of the vessels demonstrated in the present case must have been caused by hyperaemia connected with slight inflammatory changes in the lymph nodes although it is remarkable that hyperaemic lymph nodes may contain filled tortuous vessels and an accumulation of contrast medium even though there is no question of malignancy. It would therefore appear that this possibility must be borne in mind in considering the differential diagnosis.

SUMMARY

A c se is described in which filled tortuous vessels were evident in the para-aortic lymph nodes n lumbar aortography. The condition proved to be due to hyperaemia. The implications regards the differential diagnosis are discussed.

ZUSAMMENFASSUNG

Es wird ein Fall beschrieben, bei dem mittels lumbaler Aortographie geschlängelte Gefässe in den para-aortischen Lymphknoten dargestellt werden konnten. Dieser Befund scheint auf Hyperämie zu beruhen. Die Bedeutung dieses Falles, soweit er die Differenzialdiagnose betrifft, wird diskutiert.

RÉSUMÉ

L'auteur présente un cas d'aortographie lombaire où des vaisseaux tortueux situés dans les ganglions lymphatiques para-aortiques ont été injectés et mis en évidence. Il s'est avéré que cet aspect est due à l'hyperémie. L'auteur en étudie les conséquences au point de vue du diagnostic différentiel.

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PNEUMONOPLEURAL AMYLOID TUMOUR

Report of a case

by

P. LUNDIN, B. SIMONSSON and T. WINBERG

A fundamental distinction should be made between primary amyloidosis which has no known cause or predisposing factors and secondary amyloidosis which accompanies chronic infectious or degenerative processes (HERXHEIMER and REINHARDT). This classification, however, does not cover all forms of amyloidosis. The following four subdivisions of the condition were proposed by REIMANN et coll. (1) Primary amyloidosis, (2) Secondary amyloidosis, (3) Amyloidosis accompanying myeloma and (4) Amyloid tumour.

Categories (1) and (4) may be graded as primary amyloidosis as defined by HERXHEIMER and REINHARDT. The first category is characterized by deposits of amyloid, usually diffuse, in several organs such as the heart, muscles, skin, intestines, tongue and respiratory tract. The fourth category takes the form of tumour-like, circumscribed, multiple or solitary foci confined to a single organ system, usually the respiratory tract or skin.

Categories (2) and (3) are in principle secondary amyloidosis. In category (2), the most common variety, the amyloid deposits are generally found in the spleen, liver, kidneys and adrenals; in myeloma, category (3), the deposits are usually encountered in the same organs and have the same features as in primary amyloidosis.

Submitted for publication 25 August 1960.

Fig. 1

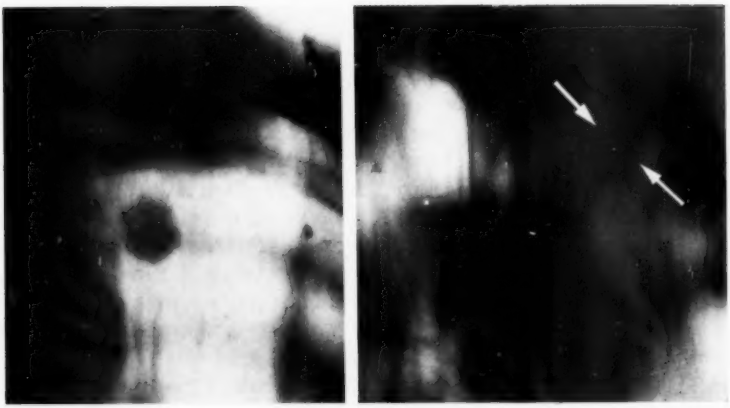

Fig. 2

Fig. 1. Homogeneous opacities, up to 3 cm in diameter, at both apices. Above they merge imperceptibly with the soft tissues of the thoracic wall and are convex and polycyclic in outline. A similar opacity, slightly larger than the end of a thumb, lies near the right lateral chest wall and another, the size of a hazelnut, in the parenchyma on the left side.

Fig. 2. Tomography in a.p. and lateral projections. Hazelnut-sized parenchymal opacity at level of 3rd rib in left dorsal region.

seems to be established that the amyloid deposits are composed chemically of protein and a sulphate-containing polysaccharide. Some workers have identified the latter substance as chondroitin sulphuric acid, but this has not been verified by others. Considering that the primary and secondary forms of amyloidosis to some extent exhibit different staining properties it is conceivable that the composition of the deposits differs from one type of amyloidosis to another. BRAUNSTEIN and BUERGER claim that three components are identifiable: protein, carbohydrate (or glykoprotein) and acid mucopolysaccharide.

Pulmonary amyloid tumours typically contain cartilaginous and osseous tissue as well as giant cells (GLAUSER). Some investigators interpret the cartilaginous tissue as bronchial wall residues (BERGMAN and LINDER).

Amyloid tumours are not very uncommon in the respiratory tract, over 100 cases being on record. They are, however, rare in the pulmonary parenchyma and pleura; we have been unable to find more than 14 cases of amyloid tumour in the pulmonary parenchyma and only one case (PROWSE) situated in the pleura.

Case report

Woman, aged 72. One sister had pulmonary tuberculosis and another sister died of lung cancer. Mass chest roentgenography in 1946 apparently disclosed no changes but in 1952 another examination revealed the presence of a rounded opacity at the apex of the left lung at the level of the 3rd rib posteriorly. It was interpreted as pleural thickening.

The patient became hoarse and had a non-productive cough in the spring of 1958. In October 1958 roentgen examination including tomography showed roughly rounded opacities, about 3 cm in size, at both apices (Fig. 1). In addition a homogeneous opacity as large as a hazelnut was observed in the left pulmonary parenchyma close to the dorsal thoracic wall (Fig. 2). Calcified deposits were present in one of the opacities on the left side (Fig. 3).

Because of these findings the patient was transferred to the Lung Clinic for further observation. She had no temperature on admission and no lymph nodes were palpable. Culture of sputum on media for growing tubercle bacilli and inoculation of guinea pigs were unsuccessful. The hemoglobin concentration and the differential white cell count were normal. No pulmonary or cardiac abnormalities were found on physical examination. The thymol turbidity test, Meulengracht's reaction, the prothrombin time, the serum alkaline phosphatase level and the glutamine oxalacetic acid transaminase all lay within the ranges of normal variation. There were no signs of albuminuria. The highest erythrocyte sedimentation rate recorded was 47 mm an hour. The electrophoretic pattern of serum proteins was entirely normal.

In an attempt to secure additional diagnostic information, artificial pneumothorax was induced on the right side. Insufflation of air caused the lung, except for an adherent apical portion, to collapse (Fig. 4). At thoracoscopy a sharply outlined, yellow, lobulated, soft mass could be seen protruding from the parietal pleura on the cupola at the side of the adhesions. A similar mass was evident in the corresponding part of the lung. A biopsy specimen was excised from the parietal protrusion. Bronchoscopy was planned but refused by the patient.

Biopsy findings. The specimen consisted of a firm, greyish-white, nearly homogeneous mass. Microscopically the tissue was mainly composed of rounded nodules of a faintly laminated, hyalin tissue, and situated immediately below the pleural mesothelium, in parts bulging out over the surface in coarsely papillar formations. The vascular walls were everywhere considerably thickened by similar hyaline tissue. Abundant cellular infiltrations were present perivascularly,

Fig. 3. Tomography. Calcified deposits in opacity at left pulmonary apex.

Fig. 4. An opacity, about 0.5 cm in diameter (arrow), persists parietally after right artificial pneumothorax.

and in the neighbourhood of the hyaline nodules, predominantly plasma cells, occasional reticular cells, and some histiocytic cellular elements were found. No giant cells could be seen. There were no signs of cartilage formation or ossification (Figs 5 and 6). Slides stained with methyl violet or crystal violet showed small areas which were distinctly metachromatic; limited areas had a definite positive periodic acid-Schiff reaction. Whereas the entire specimen was faintly stainable with Congo red, no distinct metachromasia was found in slides, stained with toluidinblue.

Seven months after discharge from hospital the patient had no symptoms or signs referable to the lungs and the roentgen appearances were unchanged.

Discussion

The essential pathologic criteria of an amyloid tumour are satisfied by the case described. In some respects the staining properties of the amyloid deposit deviated from those characterizing the common form of secondary amyloidosis (cf. BRAUNSTEIN and BUERGER).

The clinical picture is also consistent with that seen in cases of amyloid tumour. For example, there is no history of previous disease, and the site strongly suggests that this is not a case of a secondary amyloid tumour. The possibility cannot, of course, be ruled out that amyloid deposits are present in other organs, but there are no evidences suggesting that this is the case.

As in other cases of amyloid tumour published so far, our case is characterized by few symptoms. The cough which was the main reason for sending the patient for roentgen examination was not particularly severe and in due course disappeared; it may have been only a manifestation of a stubborn cold. Often centrally located tumours will give rise to a cough, while more peripheral ones, as a rule, are unaccompanied by symptoms.

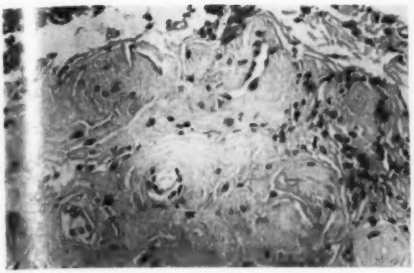

Fig. 5. Subpleural amyloid deposits in nodules and vascular walls.

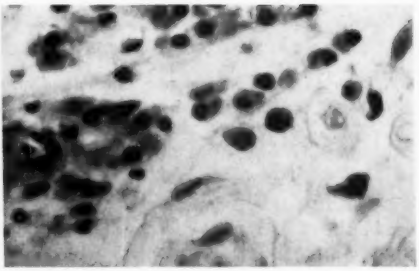

Fig. 6. Infiltrations of plasma cells in the neighbourhood of the amyloid deposits.

We were unable to arrive at a conclusive diagnosis from the roentgen findings. We were most inclined to believe that it was a matter of differentiating between tumours and inflammatory conditions, most probably tuberculosis. The rounded process in the pulmonary parenchyma alone might well be caused by a tuberculoma or a tumour. On the other hand, the pleural lesions, with their polycyclic outline and broadly based connection with the thoracic wall resembled neither a tuberculous process nor an ordinary pulmonary carcinoma or mycetoma. Tuberculous infiltrations of the lungs may be situated subpleurally but would hardly have such a broadly based attachment to the pleura. A pleural reaction to a tuberculous parenchymal process is admittedly common and may have a somewhat irregular shape, but it would scarcely have so markedly a polycyclic demarcation from the lung as in this case. Pleural tumours such as sarcoma, mesothelioma and metastases will often give rise to pleural effusions. Similarly situated malignant tumours, whether they arise from the pleura, the pulmonary parenchyma or the thoracic wall are often accompanied by pain and by destruction of neighbouring ribs and perhaps by manifestations due to pressure on the sympathetic trunk in the neck. Benign tumours seldom merge so broadly with the soft tissues of the thoracic wall. The bilateral presence of these lesions make it unlikely that they were associated with a malignant primary tumour.

Since so few cases of amyloid tumour of the lung have been reported and fewer still include roentgen findings, none of the roentgenologic features can be regarded as typical. It may be that pneumonopleural amyloid tumours are rather less rare than the literature would seem to indicate. The fact that amyloid tumours of this type have not been diagnosed more often in the past may have been due to their being diagnosed 'atypical' tuberculous processes. The need for further investigations, such as thoracoscopy with biopsy, in cases like this is apparent.

SUMMARY

A case of amyloid tumour in the pulmonary parenchyma and pleura is reported. The clinical picture, differential diagnosis and pathologic features are discussed.

ZUSAMMENFASSUNG

Ein Fall mit Amyloidtumor im Lungenparenchym und in der Pleura wird berichtet. Das klinische Bild, die Differentialdiagnose und die pathologischen Züge werden diskutiert.

RÉSUMÉ

Les auteurs présentent un cas de tumeur amyloïde du parenchyme pulmonaire et de la plèvre. Ils étudient le tableau clinique, le diagnostic différentiel et l'anatomie pathologique de cette affection.

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FRO THE MEDICAL DIVISION OF THE RESEARCH INSTITUTE OF NATIONAL DEFENCE, SUN BYBERG, THE DEPARTMENT OF PHARMACOLOGY, ROYAL VETERINARY COLLEGE, ANL THE BIOCHEMICAL DEPARTMENT OF THE NOBEL MEDICAL INSTITUTE, STOCKHOL , AND THE DEPARTMENT OF HYGIENE, UNIVERSITY OF GOTHENBURG, SWEDEN.

DISTRIBUTION OF RADIOACTIVE IRON IN PREGNANT MICE STUDIED BY WHOLE BODY AUTORADIOGRAPHY

by

SVEN ULLBERG, BO SÖRBO and CARL-JOHAN CLEMEDSON

The distribution of radioactive iron in the animal body has been previously investigated by means of autoradiography or impulse counting (COPP and GREENBERG 1946, ZILIOTTO and ODEBLAD 1955, AUSTONI, ZILIOTTO and ODEBLAD 1956, FERRINI et coll. 1957), but the technique used in the present work has the advantage of giving a general survey of the uptake of the isotope in the entire body. It also allows the detection of an accumulation of the isotope in a large number of tissues and organs that are usually not included in conventional autoradiographic methods on dissected organs. Pregnant animals were used in our investigation with the aim of studying the distribution of the iron in the mother and fetus at various times after the administration.

In addition to the general interest of an elucidation of iron metabolism, and the utilization of iron by the body in iron therapy, the present work was also initiated by the consideration of a possible occurrence of radioactive iron isotopes in bomb debris from nuclear explosions and following severe

Submitted for publication 22 July 1960.

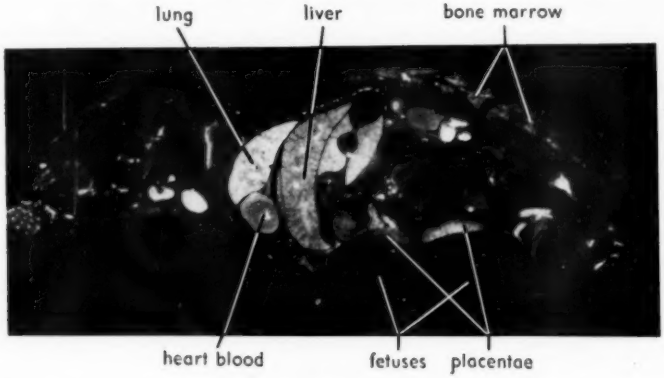

Fig. 1. Autoradiogram. Distribution of Fe^{59} in a mouse 5 min after intravenous injection of the isotope. White areas correspond to high concentration of radioiron. The isotope is mainly confined to the blood but a commencing accumulation may be noticed in the bone marrow and liver of the mother. A small amount of Fe^{59} has been taken up by the fetal blood, liver and bone.

nuclear reactor accidents; the radioactive iron may be due to neutron activation of construction details of the nuclear device or reactor shielding.

A preliminary report of this investigation was presented at the Scandinavian Summer Meeting on Biochemistry, Medical Chemistry, Pharmacology and Physiology in Turku, Finland, August 27—29th, 1959.

Methods

The Fe^{59} was obtained from the Radiochemical Centre, Amersham, England, in the form of $FeCl_3$ in 0.1 N HCl. The specific activity was in two different shippings of isotope 15 and 63 mC/mg, respectively. The ferric chloride was converted to citrate by the addition of 1 ml of 0.05 mole trisodium citrate to the isotope solution and evaporation of the latter to dryness. The residue was dissolved in distilled water and this solution was used for the injections and other administrations.

Pregnant mice, weighing from 22 to 39 g, were employed as experimental animals. One group consisting of 11 animals was used for the intravenous administration of the isotope, 0.5 μC/g bodyweight (corresponding to 0.008 to 0.03 μg Fe/g bodyweight) being injected into a tail vein. The injected volume was 0.01 ml/g body weight. These animals were anaesthetized and killed by immersion in a carbon dioxide acetone mixture (—78° C) at 2, 5 and 15 min, and 1, 4 and 24 hours, and 3 and 6 days, after administration of the isotope. In two animals radioiron was injected subcutaneously, these animals being

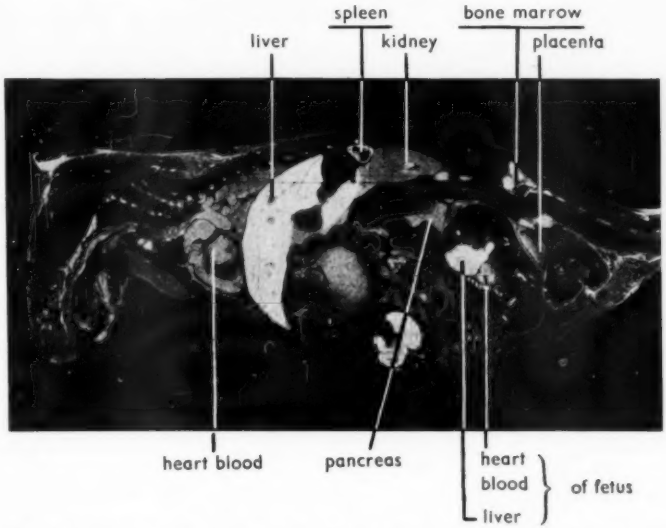

Fig. 2. Autoradiogram. Distribution of Fe^{59} in a mouse 20 min after intravenous injection. High activity in liver, bone marrow and red pulp of spleen of the mother. Higher concentration of Fe^{59} in the blood of fetus.

killed after 2 and 10 hours, respectively. Another group containing 3 animals was given 1.0 μC/g bodyweight of the isotope perorally by tube feeding. These animals were killed in the same manner as the others after 4 hours, and 2 and 4 days.

The animals were sectioned and autoradiograms were prepared according to the method developed by ULLBERG (1954, 1958). Sagittal sections, 20 μ thick, through the whole animals were made at different levels. The sections were dehydrated at —10° C and autoradiograms prepared by apposition against Gevaert Dentus Rapid film and with an exposure time of about 7 days in the first group and about 12 days in the second group.

Results

In the presentation of the results, the distribution of radioactivity in the mother and in the fetus with surrounding uterus wall, fetal membranes, and amniotic fluids, will be treated separately.

Intravenous administration of Fe^{59} — Distribution in the mother. Two minutes after the intravenous injection, all the radioiron appears to be retained in the blood. The autoradiograms obtained at that time show almost identical

Fig. 3. Autoradiogram. Fe^{59} distribution in head of a mouse 1 hour after intravenous injection. High activity in teeth, especially in the enamel of incisors and in the choroid plexus.

appearances to those produced with the same technique and showing the distribution of I^{131}-tagged serum albumin (ULLBERG, unpublished experiments). Five minutes after the injection (Fig. 1), some initial accumulation is evident in the bone marrow, liver, and red pulp of the spleen but the bulk activity still lies in the blood.

Twenty minutes after the injection (Fig. 2), the activity in the blood has decreased while the concentration in the hematopoietic organs has increased so that they stand out more distinctly. The teeth now show a very high concentration. The activity is mainly confined to the enamel of the incisors, whereas the dentin exhibits a fairly low concentration; the dental pulp has a somewhat higher activity than the blood. Other organs — the placenta and fetus being excepted — have a considerably lower activity. The concentration in the pancreas is somewhat higher than in the blood, and the basal layer of the mucosa of the stomach and intestine displays a Fe^{59} concentration that is about the same as that of the blood.

At one hour after the injection the activity in the blood has undergone a further considerable decrease. In addition to the very high activity in the dental enamel (Fig. 3) and the hematopoietic organs, the pancreas and the gastric and intestinal mucosa have a rather high concentration. A surprisingly high activity is found in the choroid plexus (Fig. 3) and in the mammary glands. Parts of the latter appear in Fig. 4 in the ventral and dorsal region of the neck due to the special arrangement of these glands in small rodents. In the pituitary and thyroid glands the amount of radioiron is lower, although it is greater than in the blood. Practically no activity is to be seen in the lymphatic tissue, thymus, the white pulp of the spleen, lymph nodes, urinary

trac and bladder, or in the central nervous system (with the exception of the cho oid plexus).

A 4 hours after the injection (Fig. 4), when the activity in the blood has rea ed its minimum, the highest concentration of radioiron is found in the bon marrow. The organs may at that time be ranged according to their deg e of activity as follows.

H gh activity: bone marrow, dental enamel, choroid plexus, red pulp of sple n, liver.

M dium activity: the mammary glands, pancreas, gastric mucosa, intestinal muc sa, salivary glands, thyroid, pituitary gland.

Low activity: lung, kidney, myocardium, lymph nodes and thymus, skeletal musc le, gastric and intestinal contents, blood, and brain (with the exception of the choroid plexus).

As is seen in Fig. 5 the highest activity in the bone is found in the marrow, but some activity is also evident in the compact bone, where it is mainly located subperiosteally.

The radioactivity in the liver is located essentially in the central parts of the lobuli. In the gastric and intestinal mucosa the highest concentration of radioiron is found in the basal layer. The activity in the gastric mucosa seems to be associated chiefly with the zymogenic cell layer. The activity in the lumina of the stomach and the intestine is very low, and there are no signs of excretion of radioiron. The bile ducts and the pancreatic duct also have a very low radioactivity. In the kidney, where the overall activity is about the same as in the blood, the activity is confined mainly to the cortex and is very low in the medulla. There are no signs of any excretion of radioiron to the surface of the skin.

Ten hours after the injection the activity in the blood is still rather low although somewhat higher than after 4 hours. The increasing concentration of radioiron in the blood obviously must be due to the commencing liberation of red cells containing radioactive hemoglobin (HAHN et coll. 1939). At one day and later after the injection the characteristic feature of the autoradiograms is the increasing concentration of Fe^{59} in the blood. Three days after the administration of the isotope the activity in the blood is still somewhat lower than in the bone marrow. After 6 days, however, the activity is higher in the blood than in the bone marrow, which indicates that the majority of red cells containing radioactive iron have already left the latter. The activity decreases earlier in the liver than in the bone marrow. In the red pulp of the spleen the concentration of radioiron remains high for a considerable time. The dental enamel retains a high activity throughout the time of observation.

Three days and 6 days after the administration of the isotope, an accumulation of Fe^{59} can be observed in the brown fat tissue. The activity in the mammary gland, on the other hand, has decreased at that time.

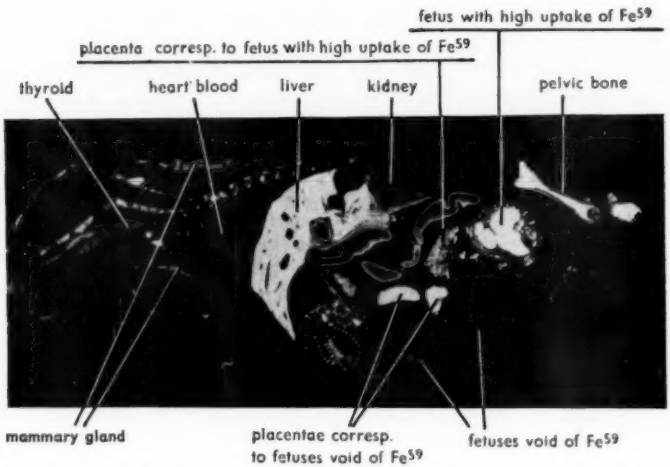

Fig. 4. Autoradiogram. Distribution of Fe^{59} in a mouse 4 hours after intravenous injection. Almost all the isotope has left the blood. Two fetuses show no uptake of radioiron; the corresponding placentae have an extraordinarily high radioactivity.

Distribution of Fe^{59} in the fetus. No radioactivity has been found in the fetus at 2 min after the injection, but traces of activity which are confined to the blood and the liver and fetal bone are evident after 5 min. As early as 20 min the concentration of radioiron in the blood of the fetus is higher than that in the blood of the mother, and the fetal blood activity thereafter remains considerably higher than in that of the mother during the whole observation period.

The distribution of the isotope in the fetus is different from that in the mother in the following respects. The activity in the liver is much more dominating in the fetus than in the mother; the fetal bone marrow displays a comparatively low activity especially in the central parts of the marrow, and the central nervous system of the fetus has a higher uptake than that of the mother. The high activity in the fetal liver is probably due to its hematopoietic function. The accumulation of radioiron in the choroid plexus of the fetus is remarkably high.

The placenta shows a fairly high uptake immediately after the injection, and it still retains a high concentration 24 hours after the administration.

In the mice killed up to 20 min after the injection the activity is fairly evenly distributed in the chorio-allantoic placenta, but later on an additional still greater accumulation appears on the inner margin facing the fetus and which seems to correspond to the visceral yolk sac epithelium.

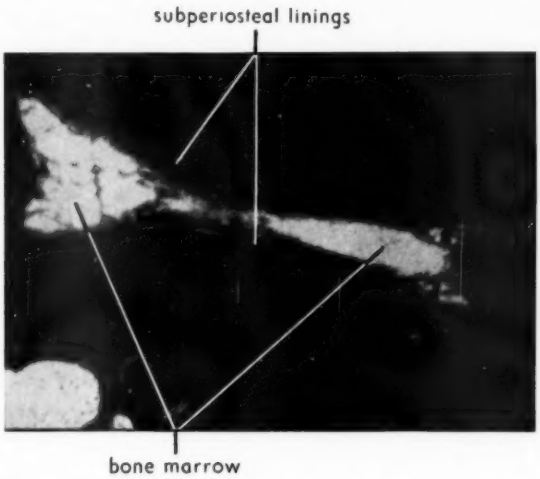

Fig. 5. Detail from fig. 4 showing uptake of radioiron in bone marrow and in subperiosteal lining of a pelvic bone.

Peroral administration of Fe^{59}. The distribution patterns after peroral administration were largely similar to those after intravenous injection. One notable exception, however, is that the radioiron did not accumulate in the liver of the mother (Fig. 6), the concentration in the liver being lower than in the blood. In the liver of the fetus, on the other hand, an appreciable accumulation was seen, and the concentration appeared to be of the same magnitude as in the cases of intravenous injection.

Four hours after the administration rather large amounts of the isotope were still present in the intestinal contents, while at later times the radioiron content of the intestines was only insignificant.

Subcutaneous administration of Fe^{59}. The distribution of radioiron in the mother after subcutaneous administration of the isotope was also essentially similar to that after intravenous injection. A remarkable observation, however, was that as in the case of peroral administration the uptake in the liver was very low or almost nil.

Discussion

The present investigation clearly demonstrates that the radioiron is leaving the blood stream and is taken up in the tissues rather slowly in comparison with other metabolites such as amino acids, which are almost completely cleared off from the blood within the first ten minutes after their intravenous administration.

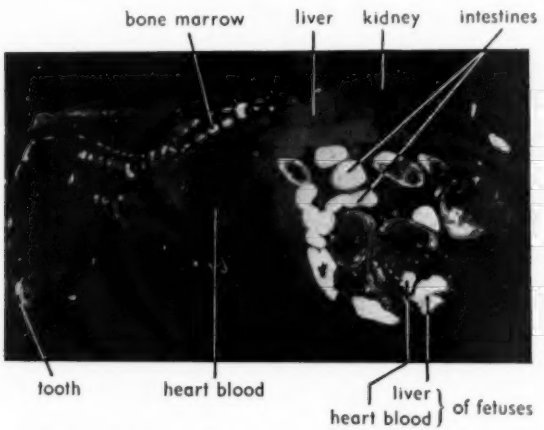

Fig. 6. Autoradiogram. Distribution of Fe^{59} in a mouse 4 hours after peroral administration. Low uptake in maternal liver but high uptake in fetal liver. High content of radioiron is still present in the intestine.

The general distribution patterns of radioiron in the body found in this study is, as far as the blood and the hematopoietic organs and the intestinal mucosa are concerned, essentially in agreement with the results obtained by other investigators by means of impulse counting or autoradiography on dissected organs (HAHN et coll. 1939, AUSTONI and GREENBERG 1940, GRANICH and HAHN 1944, COPP and GREENBERG 1946, AUSTONI, ZILIOTTO and ODEBLAD 1956). The high concentration of the isotope which could be demonstrated in some other organs, however, merits some discussion.

The considerable accumulation of iron in the teeth is of particular interest. The rapid uptake of the isotope from the blood stream in this tissue seems to indicate that the iron in the teeth is present essentially in the inorganic form. The isotope lies especially in the enamel, and it should be noted that its distribution in the teeth shows a picture similar to that of radiostrontium and other bone-seeking isotopes (ENGSTRÖM et coll. 1958). It has been demonstrated earlier that the incisors of rodents have a fairly high content of iron but its physiologic significance is not known.

The heavy uptake of radioiron in the choroid plexus is of great interest as regards the possible metabolic function of this structure. The physiologic significance of the high iron uptake of the plexus is, however, unknown.

Of particular interest is the high concentration of radioiron found in the salivary, mammary, thyroid and pituitary glands. As far as the three first-mentioned glands are concerned, their high iron uptake may perhaps be related to

their known content of peroxidase (ASTWOOD 1955). In comparison with other iron sources in the body, however, enzyme iron represents only a small part, probably less than one per cent. Nothing seems to be known so far about the physiological role of the iron in the pituitary gland. The fairly high uptake of radioiron by the pancreas, which was demonstrated earlier by ZILIOTTO and ODEBLAD (1955), has been confirmed by the present study.

TABIANA et coll. (1959) found a high concentration of parenterally administered radioiron in the intestine and suggested an intestinal cycle with secretion and re-absorption of the isotope. The present investigation does not support these findings. In accordance with COPP and GREENBERG (1946) we found no appreciable excretion to the intestinal lumen of injected radioiron. Nor has any significant excretion been found to take place through other possible routes, such as through the kidneys, biliary and pancreatic ducts or to the surface of the skin.

The observed distribution of Fe^{59} in the placenta and fetus is in large in agreement with the results of other investigators (VOSBURGH and FLEXNER 1950, CAMPBELL and NYLANDER 1951, NYLANDER 1951, 1953, VON EHRENSTEIN and HEVESY 1956, DAVIES et coll. 1959).

The fact that the fetal blood has a considerably higher concentration of radioiron than the maternal blood as early as 20 min after the injection is in accordance with the findings of VOSBURGH and FLEXNER (1950). They suggested that iron is transferred from mother to fetus as serum iron and that the maternal red cells are not an important source for the fetal iron. It also seems to speak in favour of the passage of iron through the placenta being an active process.

A peculiar finding in the autoradiogram of one animal that was killed 4 hours after the injection of the isotope was that two of its fetuses had taken up no activity at all. The corresponding placentae, on the other hand, showed a very high concentration of radioiron, their activities being several times higher than the activity found in those fetuses that had taken up radioiron in the usual extent. The microscopic appearance of those fetuses that did not show any uptake of radioiron was normal and did not differ from the others in respect to size and stainability, for example. No explanation for this placenta-fetus blockage to iron passage could be found. It should be noted in this connection, however, that VOSBURGH and FLEXNER (1950) have found that there may be a considerable difference in the amount of iron transferred to members of the same litter during the course of an experiment.

The strong accumulation of radioiron in the fetus is of significance from the standpoint of radiation hazards in human iron metabolism studies with radioactive iron and in accidental exposure. The most potent isotope is Fe^{59}, which is classified as highly dangerous, while Fe^{55} is classified as dangerous. The critical organ of the fetus for radioiron seems to be the liver, which has an important hematopoietic function in the fetus. As shown by VON

EHRENSTEIN and HEVESY (1956), 73 to 83 per cent of the total iron content of the fetus is located in the liver. In the adult, the gastrointestinal tract and the spleen are listed as the critical organs (ICRP 1959).

In addition to the bone marrow which is highly radiosensitive in the mother as well as in the fetus, the choroid plexus and the placenta should be kept in mind as possible critical points since it is probable that the corresponding structures in the human subject also have the ability to concentrate radioiron.

The maximum permissible total body burden for Fe^{59} according to the recommendations of the ICRP (1959) is 20 μC. For iron metabolism studies by means of radioactive iron VEALL and VETTER (1958) state that after a dosage of 20 μC to an adult person, the total dose will not exceed 1.5 rad distributed over a time interval of 9 weeks.

SUMMARY

Fe^{59} was administered intravenously, and in a few experiments perorally and subcutaneously, to groups of pregnant mice, and the distribution studied in sections of the whole animals by an autoradiographic technique. The uptake of the iron in the organs of the mother and fetus at various intervals is described and discussed.

ZUSAMMENFASSUNG

Gruppen schwangere Mäuse erhielten Fe^{59} intravenös und in wenigen Experimenten peroral und subkutan. Die Verteilung des Isotopen wurde in Sektionen des ganzen Tieres mit Hilfe einer autoradiographischen Technik studiert. Die Aufnahme des Eisens in den Organen der Mutter und des Fötus zu verschiedenen Zeitpunkten der Schwangerschaft wird beschrieben und diskutiert.

RÉSUMÉ

Du Fe^{59} a été administré par voie intraveineuse, et dans quelques cas, par voie buccale et sous-cutanée, à des groupes de souris gravides; sa répartition a été étudiée sur des coupes totales du corps de ces animaux par une technique autoradiographique. Les auteurs décrivent et étudient la fixation du fer dans les organes maternels et foetaux à différents stades.

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Book reviews

STRAHLENBIOLOGIE, STRAHLENTHERAPIE, NUKLEARMEDIZIN UND KREBSFORSCHUNG. Ergebnisse 1952—1958. Herausgegeben von H. R. Schinz, H. Holthusen, H. Langendorff, B. Rajewsky und G. Schubert. 998 Seiten, 395 Abbildungen und 140 Tabellen. Georg Thieme, Stuttgart 1959. Price: DM 275.

With the object of carrying on the tradition from "Ergebnisse der medizinischen Strahlenforschung" of providing radiotherapists and radiobiologists with reviews of the developments in their special fields this book presents a series of short monographs on subjects related to radiobiology, radiotherapy, nuclear medicine, and cancer research.

Four chapters are devoted to radiogenetics, and one chapter, presented in readily comprehensible terms by WIDERÖE, the designer of the asclepitron, deals with the physics and technique of megavolt radiation. Experiences with the 31 MeV betatron in Zürich, described by COCCHI, should be of interest to all working with million volt treatment. The chapter on radiomimetic substances is rather short and would have been more complete if it had contained case reports and photographs of patients taken before and after treatment.

The treatment of bronchial cancer by radiation is discussed by HELLRIEGEL, who also describes three cases of lung cancer in which the patients were alive three years after treatment. Isotope diagnosis in diseases of the thyroid gland is described exhaustively by HORST, and isotope treatment by GAUWERKY, both from Hamburg.

The work may be regarded as a reference book with an extensive bibliography.

Folke Jacobsson

CINEFLUOROGRAPHY. Proceedings of the First Annual Symposium on Cinefluorography, 1958. Edited by G. H. S. Ramsey, J. S. Watson, T. A. Tristan, S. Weinberg and W. S. Cornwall. 266 pages, 142 figures and 8 tables. Charles C. Thomas, Springfield, Ill., 1960.

Considerable interest is shown by radiologists and others in cinefluorography for evaluating normal and abnormal anatomy and physiology. The First (1958) Annual Symposium on Cinefluorography at the University School of Medicine and Dentistry, Rochester, was well attended and the Proceedings form an attractive book, being of special value as both elementary problems and latest developments have been included.

The answers to questions during the discussion following the various papers have been carefully edited, and thus the complete discussion can be followed — an arrangement providing much of value to the reader.

In the introductory chapters a general view of the methods of cinefluorography, image intensification, and the application of television to cinefluorography are presented. Recording equipment and photographic aspects are also considered and the problem of the radiation dose in image intensifier cinefluorography is discussed. Special chapters are devoted to the projection and diagnostic analyses of cinefluorograms.

Not only are more conventional methods of cinefluorography discussed but new and more special procedures such as the use of solid-state amplifying screens, fibre optics and less conventional image amplifiers are also considered. The illustrations, based on slides and films of educational clarity, as well as the printing, are of very high class.

The book provides concentrated information on the problems involved and is warmly recommended to all radiologists.

Ove Matts

MEDICAL X-RAY TECHNIQUE. By G. J. van der Plaats. 492 pages and 213 illustrations. Philips Technical Library, Eindhoven 1959. Price: Sw. Kr. 41:50.

This book is stated to be a text-book for all concerned in the medical use of roentgen rays in diagnosis and therapy and particularly for student radiographers. Both roentgen and isotope problems are treated. The author of the book is wellknown to most radiologists and this exhaustive treatise on the principles and applications of medical roentgen technique bear the mark of solid knowledge.

The production of roentgen rays, roentgen tubes, and the properties of roentgen rays are discussed in an introductory chapter. The methods of image formation and laws of projection as well as resolution of detail and problems of definition are examined thoroughly. The photographic problems including contrast, exposure and processing are considered in separate chapters and different apparatus as well as radiographic techniques are exhaustively described; electrical wiring diagrams are included. The biologic effect of radiation, dosimetry, different types of radiation therapy, and isotopes are discussed in turn. The final chapter deals with "the radiation hazards and protective measure in roentgen diagnosis and therapy".

The book provides the reader with valuable information not only confined to routine practice. Concentrated data of a more special character appear in small print. But yet, in some respects, one misses more detail. Developing machines, image intensifiers, and cinefluorographic techniques have, for example, been dealt with rather summarily. The illustrations are really excellent.

This book is recommended to all who are entering roentgenology although it is also of value to others as a reference work. No modern book of such a comprehensive nature has been available until now.

Ove Mattsson

WILHELM CONRAD RÖNTGEN UND DIE GESCHICHTE DER RÖNTGENSTRAHLEN. Von O. Glasser. Mit einem Beitrag 'Persönliches über W. C. Röntgen' von M. Boveri. 2. Auflage. 381 Seiten, 112 Abbildungen. Springer-Verlag, Berlin-Göttingen-Heidelberg 1959. Price: DM 58.

A second edition has now appeared of Dr. O. Glasser's well-known book on W. C. RÖNTGEN and the history of roentgen rays. A number of additions and improvements have been made but the main character of the book is unchanged. The life of RÖNTGEN is reported as fully as available sources permit. A long contribution by Miss M. Boveri: 'Personal data on W. C. Röntgen', in which important and valuable information is mingled with long versified dinner speeches and other matters of limited interest, is included. Dr. Glasser duly stresses the often forgotten fact that RÖNTGEN was a highly renowned physicist and had made important contributions to science long before the discovery of roentgen rays in 1895.

The history of roentgen rays and their uses in various sciences including medicine, technology, and other spheres of activity are in this book mainly confined to the year 1896, from which year no less than 1 044 books, brochures, and papers in scientific journals are listed. The references from later years number 86. The reaction of the scientific world and of the general public to the discovery is described in great detail; this is sometimes amusing but at times boring. The reprints of RÖNTGEN's own three papers of the period 1895—1897 are in a class by themselves: brief, clear, and concise. It is surprising to see how much scientific and technologic progress of the following decade was anticipated in these early papers.

Sven Benner

THE TOMOGRAM. ITS FORMATION AND CONTENT. By Paul Edholm. 109 pages and 74 illustrations. Acta radiol. (1960) Suppl. No. 193. Sw. Kr. 30.

This book is aimed at an analysis of the influence in tomography of the type of tomographic movement employed, the size of the tomographic angle, and the distance between the tomographic plane and the centre of the object, as well as the absorption of the object.

The apparatus, radiation, and film were standardized by the use of mathematic models so that curves showing the density distribution (the image relief) in the tomogram could be calculated. These calculations were performed for circular and linear tomography of a sphere and a cylinder for different values of the factors enumerated above. An electronic digital computer was employed. The images represented by the calculated curves were assessed by applying physiologic principles underlying the perception of contour and contrast. The variations of contour sharpness and contrast in the tomogram under different conditions are shown in the book by means of graphs. It was possible to construct image relief curves for tomograms of other objects with the aid of the curves calculated for the sphere and cylinder.

A quantitative assessment of the distortion of the image caused by tomography under various conditions was among the results obtained. It was found that large tomographic angles considerably distort the image so that sharpness and contrast are much reduced; when the object tomographed is a hollow organ with a thin wall this reduction of sharpness and contrast becomes marked.

Discrepancies between the mathematic models used for the calculations and practical tomography are discussed and the effect of some of these are calculated.

Tomograms were obtained experimentally, under conditions corresponding as far as practicable to those for which the calculations were valid, in order to test and supplement some of the theoretical conclusions; densitograms that represented the image reliefs were made from the films. Tomograms of spheres and cylinders were produced with commercial apparatus in a second series of experiments.

Autoreview

LOW-LEVEL IRRADIATION. Edited by Austin M. Brues. 158 pages, 18 illustrations. American Association for the Advancement of Science, Washington 1959. Price $ 3.75.

This booklet consists of papers read at a symposium of the American Association for the Advancement of Science in cooperation with the U. S. Atomic Energy Commission and the Argonne National Laboratory in December 1957. In contrast to most other treatises of this nature, the book deals not only with radiation levels and various biologic effects of radiation for almost as much space is devoted to their implications for human relations in general.

The first part, 'Scientific Background', after a short introduction by E. L. POWERS, begins with a paper by R. E. DUDLEY on natural and artificial radiation levels, showing how little the much discussed fall-out radiation means, at least as yet, in comparison to natural and medical radiation. L. MACHTA reviews meteorologic facts of importance for the distribution of radioactive fission products from nuclear weapons tests over the earth. E. L. GREEN summarizes genetic effects and the editor deals with the somatic effects of radiation. The difficult task of giving in the very limited space the essentials of what we know, and what we need to know, seems to have been very well solved.

The second part, 'Implications', is introduced by the editor, whereafter D. E. PRICE looks at the problems as a public health administrator from a non-technical viewpoint. A. J. STONIER writes on the responsibility of the press to provide the public with well-balanced information on these difficult questions. C. HOLIFIELD treats legal and political implications, and C. W. CHURCH-

MAN discusses the intricate problems of the morals of science. The book ends with a summary and conclusions by the Editor.

The book is very well worth reading and is thought-provoking as a general consideration from many different viewpoints of questions of great importance, possibly in the future life- or-death ones for humanity.

Sven Benner

THE TREATMENT OF BRONCHIAL NEOPLASMS. By Robert R. Shaw and Donald L. Paulson, with a chapter on bronchial adenoma by John Lester Kee, Jr. 135 pages, 63 illustrations and 10 tables. Charles C. Thomas, Springfield, Ill. 1959. Price: $ 8.

The authors of this book point out in the introduction that in spite of intensive propaganda for early diagnosis the operability figure for lung cancer has not shown much improvement during the past few years. The number of operable cases is approximatively the same among both 'early' and 'late' cases. The authors consider that the time factor is of lesser significance than the biologic factors in the prognosis for lung cancer.

The conclusions are based on a material of 1 180 cases of cancer of the lungs. Approximately two-thirds of the cases were inoperable and consequently had to be treated by methods other than surgery. Radiation treatment stood first as the method of choice in these cases, mainly as a palliative measure. The authors state that it was possible with radiotherapy to reduce or even entirely eliminate the atelectasis and hence bring considerable relief in the dyspnoea and cough. Particularly in compression of the vena cava radiation treatment usually produced a rapid and as a rule permanent improvement in the troublesome symptoms.

Naturally enough, seeing that the authors are surgeons, the greater part of the book is devoted to a discussion of the selection of patients for operation and different operative methods. One chapter, however, deals with the possibilities offered by radiotherapy in the treatment of lung cancer, and contains good reproductions of roentgenograms taken before and after treatment. An inoperable case given radiation treatment and alive six years later, free from symptoms and at work, is described in some detail. The roentgen technique employed for the treatment is not mentioned, however. A short chapter is devoted to chemotherapy, and in conclusion the authors give a brief review of bronchial adenoma, a tumour group which, though small, is of considerable interest from the biologic and differential diagnostic points of view.

The book presents a clear picture of the treatment possibilities in cancer of the lungs together with both comprehensive and well-reproduced illustrations.

Folke Jacobsson

DETAILERKENNBARKEIT UND DOSIS BEI DER RÖNTGENDURCHLEUCHTUNG. Von W. Frik. Medizin, Theorie und Klinik in Einzeldarstellungen. Band 6. 168 Seiten, 35 Abbildungen und 48 Tabellen. Alfred Hüthig Verlag, Heidelberg 1959. Price: DM 18.

This monograph deals with the ideal conditions for fluoroscopy of the chest with special reference to the dose and the information such an examination can yield.

The experimental arrangement consisted of plexiglass or sugar-paraffin bodies in the shape of Landolt's rings, beads or truncated cones, placed in front of or behind plexiglass phantoms or thin-walled vinidur chambers containing water. The initial roentgen factors employed were 55 kV and 3 mA with a total filtration corresponding to 2 mm Al. This value was chosen on empirical grounds as the lowest possible for satisfactory fluoroscopic examination of the chest. The examination conditions were varied in different ways according to the filtration, screen

emulsion, focus, type of generator, and strength of voltage and current. The most satisfactory combination was found to be 90 kV from a 6-valve apparatus, 1 mA, and filtration corresponding to 6 mm Al. The best fluoroscopic screen contained 100 mg ZnCdS per cm² with 62.5 % ZnS. In all examinations a focus-screen distance of 70 cm was used. Fluoroscopy under these optimal conditions gives a low skin dose and a low volume dose. The percentage increase of the gonad dose is fairly high, but the absolute gonad dose is nevertheless so small that it may be neglected.

On fluoroscopy with a Philips 5-inch image intensifier it was found that the perception of well-defined details was twice as good, while less well-defined details were not so readily recognised as in ordinary fluoroscopy. The reduction of the radiation dose was very small. Fluoroscopy with less than 1 mA and a focus-screen distance of 70 cm involves the risk of very disturbing quantum fluctuations especially by dense objects.

Unfortunately the language is inclined to be cumbersome and the author's meaning is not always clear; in addition, calculations and surveys of numeric data are rather scanty although they can be readily deduced from the information given. But with these reservations it may be said that the views presented by the author are valuable and deserve consideration.

Thure Holm

DIAGNOSTIC RADIOISOTOPES. By Charles A. Owen, Jr. 425 pages, 71 figures and 49 tables. Charles C. Thomas. Springfield, Ill., 1959. Price $ 15.75.

It is stated in the preface that 'the literature on medical applications of the radioactive isotopes is concerned primarily with treatment and only incidentally with the diagnostic tests'. This seems to be an overstatement for the reviewer recalls books, even from the same publisher, which were similar to the present one and in which the emphasis was on diagnostic usage. Be that as it may, the book is nevertheless quite valuable and to be recommended as a good introduction to modern radioisotope diagnostics. Its use presupposes, however, some previous knowledge of radiation physics, radiation detectors, and radiation protection, subjects which are but briefly treated. Attention in the main is paid to a detailed description of the practical performance of the more important tests and on the calculation of the results.

The matters most fully treated are the use of radioiodine for metabolic studies, chromium and iron in hematology, and the localization of tumours, and long lists of references add to the usefulness. In reading the longer chapters it is, however, rather difficult to find the references to the particular chapter, as the chapter headings are not, as is usual, given at the top of the pages.

A number of the other uses of radioisotopes are described more briefly although the references indicate to the interested reader where he can gather further information. Tables of the known radioisotopes and of the decay of the more important ones at various times as well as of logarithms conclude the monograph.

Sven Benner